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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
April 19, 2006
Marriott Hotel Seatac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D
Robert Bray, MD
Carol Cordy, MD (Vice Chair)
Jason Iltz, Pharm D
Janet Kelly, Pharm D
Daniel Lessler, MD (Chair)
T. T. Vyn Reese, M.D.
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

9:00 a.m. - Committee came to order.

Dan Lessler: Good morning. We can get started here. Dan Lessler, I'm the chair of the P&T Committee and I think actually we have some guests today. So I thought actually maybe we could begin just with introductions of our guests and then the committee could just go around and introduce themselves. So Duane maybe you could begin.

Duane Thurman: Thanks. This is Duane Thurman. Remember speak into the mikes for our transcript, please. Sitting next to me is Lea Hole-Curry and she's the new director for the Health Technology Assessment Program at the Health Care Authority and it's her…she's going to be joining our efforts to bring evidenced-based medicine to a whole 'nother area. So I just wanted her to come here and meet people and see how our process goes and we'll be working closely to try to be successful in that one.

Lea Hole-Curry: Thanks. It's a pleasure to be here and I'll be interested to see how the committee works together. As Duane said, we'll have to form our own clinical committee for the Health Technology Assessment Program. So I'm just interested in the process and appreciate being a part of it.

Dan Lessler: If you're here maybe at lunch time I'm sure committee members might have words of wisdom as well to help you out. And then let's see we have…Jeff, I think…

Jeff Graham: I would like to introduce Dr. Allison Little who I believe is sitting in the back there. Allison is the Medical Director for the Center for Evidenced-Based Policy at Oregon Health and Sciences University. She is filling the position with John Santa previously and has moved onto another position there. So we have our contract through that center. So we're very pleased that she's here today.

Dan Lessler: Thanks. Welcome. And it sounds like we have OHSU on the phone there maybe.

* For copies of the official audio taped record of this meeting, please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

Rick Hanson: Yeah, this is Rick Hanson actually calling in from UNC in North Carolina.

Dan Lessler: I'm sorry. Rick, this is Dan Lessler. Thanks for calling in. Before we get started here actually we're just going to call up the…do we have slides for the…we're just getting your slides projected here and I'll let you know in a second when we are ready to go.

Rick Hanson: Okay, sounds great.

Dan Lessler: And Jeff I was going to…I didn't know if there were any other announcements or anything that you had administratively?

Jeff Graham: I don't believe we have any other announcements today.

Dan Lessler: All right. Okay. Rick, we're set. Right now we are looking at your title slide from your PowerPoint and you can take it from there and just tell us when you want to go to the next slide.

Rick Hanson: Okay, sounds great. Now what I planned to do…I sent you the pretty lengthy list of slides here and if it's alright with everyone there what I wanted to do is go through a number of things, but focus really on what was included in the update and where that changed any conclusions that we might have had.

Dan Lessler: That would be fine.

Rick Hanson: That's fine. Okay. And I saw that I've got almost an hour, but I sort of planned this for about 20 to 30 minutes if that works.

Dan Lessler: That works.

Rick Hanson: Okay. So I'll start on slide two then. The original review included five different drugs and the update specifically added mometasone as a dry powder inhaler so we ended up actually re-doing the search going back because a lot of the studies with mometasone had been done some time ago. They weren't exactly all recent studies. So we went back and we did our entire search looking back for all six drugs. Slide three we focused specifically on adult and pediatric outpatients with asthma and then on adult outpatients with COPD.

Slide four none of the outcomes specifically changed, but just to go over how we handled them. We specifically looked for health outcomes rather than intermediate outcomes and what we…how we defined that was looking at things that directly effected the patient or their ability to function such as alleviation of symptoms, quality of life, ability to participate to participate in work, school or physical activity. We looked at emergency department or urgent medical care visits as a utilization variable. We looked at hospitalizations and also mortality and after our initial view of the literature because a lot of the health outcomes were not reported in COPD studies we also did include some intermediate outcomes such as lung function tests for the COPD population.

Slide five for tolerability or safety we looked at overall adverse effect reports, withdrawals because of adverse advents, serious adverse advents, and specifically under the serious adverse event category we looked for evidence of osteoporosis, growth reduction or retardation as I have it there, acute adrenal crisis, cataracts and ocular hypertension and open-angel glaucoma.

Slide six we included different studies in our review and basically for effectiveness or efficacy in just to differentiate that the two…we did apply criteria to try to get at studies that we felt were generalizable to a broad population versus efficacy studies that might be conducted in a more narrowly defined population. So you might hear me refer to that as I go through this. And I'll just note that the effectiveness evidence we deemed to be more generalizable and thus could have potentially more impact for a broad treatment population. We included head-to-head trials, meta-analyses, and placebo-controlled trials. And then we also included observational studies although we tended…when there was sufficient randomized evidence we tended to give the observational evidence less weight. For safety and adverse events we again included head-to-head trials, meta-

analyses, placebo-controlled trials, and then observational studies. In sub groups all of the above for sub groups.

Slide seven this is something that I believe I presented to this group last year and discussed, but what we did is…although we didn't use dose or device considerations in our quality assessment; in other words studies could compare unequivalent doses and still be given a similar quality rating, but we did make sure to go through and point out when doses were not equivalent. So for instance there's the NAEPP dosing guidelines. Basically what this reflects is given the difference in potencies with the drugs what are relatively comparable doses? For instance, what's a low dose, a medium dose or a high dose? And then we took it a step further and said, "How many puffs per day would you need to deliver a comparable dose?" And then we used that as an indicator in our evidence tables to say, for instance, that head-to-head trials compared lower dose to lower dose or medium dose to medium dose and this really…these dosing guidelines aren't an exact science. There's going to be variations in how patients use the inhalers and thus there could be, you know, there's some degree of I guess lack of confidence in a medium to a medium dose. We just used this as a guide to make sure we were comparing apples to apples. So we used the NAEPP for our previous review because mometasone was added and it is not yet in the NAEPP guidelines we used the International Primary Care Airways Group, which provides us similar stratification of dosing. So that's how we classified mometasone here. And then in one of the additions with this review was that because we felt that the number of doses per day and the number of actuations per dose…delivered a dose differs we did a search also to look for if there's any evidence that for instance once daily versus twice daily dosing effects outcomes or if for instance different devices have an impact on outcomes and that…we included an addendum to the full report.

Moving on to slide eight, for a comparative effectiveness, again, this would be the more generalizable evidence. We did not find any head-to-head trials that met our effectiveness criteria. We did have 24 head-to-head trials that we determined to represent comparative efficacy. This was five additional trials from our previous review all of which focused on mometasone. We had one meta-analysis that was included in our previous review and then for general efficacy, again, this is focusing specifically on quality of life or functional capacity, which were outcomes that were infrequently represented in comparative trials. We found two additional studies for a total of 12 placebo-controlled trials.

On slide nine looking at just the comparative evidence our conclusions was that the evidence-base was mixed and for the most part on most outcome measures evidence supported no difference when comparing one drug to another when used at a comparable dose. Fifteen of 24 studies however did report significant differences on at least one of the outcome measures and I just noted here most often this favored fluticasone over the comparator and I'll just add to that that mometasone also given that it's a more potent agent also fell into this category also fluticasone seemed to be more consistently favored.

So the next two slides, slide 10 and 11 basically what I did here is just sort of provide all of the studies in a table here to show you a little bit about where some of these outcomes differed. So slide 10 reflects specifically beta-agonist use as an outcome measure and in the left column those are the comparisons with BDP representing beclomethasone, BUD – budesonide, FLUP – fluticasone, MOM – mometasone, TRIA – triamcinolone and FLUN – flunisolide. Sorry about the abbreviations. So those are the comparisons. And then in the next column you'll see the number of trials that we included in our review for each of those comparisons and the subsequent column reflects trials with no differences while the last column represents trials that did demonstrate a difference with the greater sign representing for instance beclomethasone versus fluticasone. The second row of that table you see that two of seven trials found fluticasone to be significantly better than beclomethasone.

In looking at this evidence though going back to the dosing equivalence some of the trials did not compare equivalent doses. For instance, one budesonide versus fluticasone study used higher doses of fluticasone and both of the fluticasone versus triamcinolone studies utilized higher fluticasone doses. So that's a consideration that does need to be taken into account when reviewing the evidence.

In slide 11 this table set up similarly to the previous table so again reflecting the number of studies that reviewed asthma symptoms as an outcome. And usually this was using the symptom score that ranged anywhere from a three point to a seven point scale representing the degree of symptoms the patient was experiencing and again a number of studies did show differences although most did not show any differences statistically that is. And again some of the doses weren't equivalent. For instance, the beclomethasone versus triamcinolone study used a higher dose of beclomethasone. Mometasone versus budesonide both of those studies used a higher mometasone dose and the fluticasone versus mometasone study that study used a higher dose of fluticasone. So, again, some of the differences may be related to dose equivalency or lack thereof.

Moving on to slide 12, this slide summarizes a meta-analysis that we included in the earlier version of this report and it is still worth emphasizing. What this study did is they pooled trials that represented beclomethasone and budesonide with the logic that those were two of the less potent agents and compared it to fluticasone and in this particular meta-analysis, which we rated as good there were no differences in asthma symptoms, exacerbations or beta-agonist use. Although this again is comparing fluticasone to the pooled affect of beclomethasone and budesonide so it's not really providing individual comparisons.

Slide 13 shows how limited the evidence was for quality of life or functional status and this was just the comparative evidence. So for instance there were four studies that compared one drug to another, all comparing fluticasone to a competitor and in this particular table I organized it a little bit differently. The second column shows the results while the third column summarizes whether or not the doses were different. So for instance fluticasone versus beclomethasone there were no differences in the asthma quality of life questionnaire, which is a measure of quality of life. Fluticasone versus budesonide…the fluticasone treated patients had fewer days absent from work and those doses were equivalent according to the NAEPP guidelines. For fluticasone versus budesonide again another study found no differences in missed school and fluticasone treated patients had fewer disruptions in activity and then a fourth study found greater improvement in the asthma quality of life questionnaire for fluticasone treated patients. So evidence that fluticasone favored the competitor although again some of the studies did have slightly higher fluticasone doses likely driven by its higher potency.

Slide 14 – this slide just summarizes the placebo-controlled evidence that we included looking at quality of life for functional status. Basically we added a couple of additional studies all focusing on mometasone with the inclusion now being that there is evidence that these drugs do significantly improve quality of life for functional status when compared to placebo and you can add mometasone to that list.

Slide 15 then summarizes our conclusions for asthma. We did say that the evidence was mixed with regard to whether or not one drug is different from another. For the most part, as I covered just recently, the differences seemed to be related to potential differences in dose or delivery device although it's tough to say that for certain so we rated the overall evidence as fair. In other words we think more needs to be done to sort of get at some of these potential differences and the effect of dose and delivery devices effect on outcomes.

Slide 16 moving on to COPD we did not include any new evidence for COPD and thus I was…here is one of the places I was hoping to move ahead and skip through to slide 22 although I'll just briefly summarize our conclusions. Again, we were only reviewing monotherapy-inhaled corticosteroids so combination products did not make the list here. So there were not any other products that we reviewed as monotherapy approved for treatment of COPD. We didn't find any comparative studies and only 13 placebo controlled trials that addressed general efficacy and three meta-analysis although there have been a couple meta-analysis published since then that can add to this that were after our…this review was conducted.

For general efficacy there's fairly good evidence that inhaled corticosteroids do not reduce the risk of overall mortality. This has been debated in the literature though and the evidence is actually difficult to interpret given the types of studies that are available for this question.

Quality of life – the majority of trials did not detect any significant differences in quality of life between drug…or between an inhaled steroid and placebo although there is some evidence for instance one study reported significantly slower decline in quality of life in patients with severe COPD that were on high dose fluticasone.

So actually I'm going to move on then to slide 21 just to summarize for COPD. The evidence is fairly poor. There really is not any consistent evidence that we can…that looks at one drug compared to another and even placebo controlled trials they are insufficient to draw conclusions here.

Slide 22 looking at tolerability and discontinuation rates…looking at head-to-head evidence we did not find any differences in overall discontinuation rates. They are discontinuations because of adverse events. In general the rate of side effects was relatively low. Most of the side effects that were reported we coined to be local side effects. In other words things like oral candidiasis, rhinitis, cough, hoarseness, bronchitis and sore throat and the incidents of those side effects was generally less than 10%. There were a couple of studies that looked at upper respiratory tract infections and reported slightly higher incidents of these infections particularly in pediatric populations although we don't have any strong evidence to suggest that that is the reason there, just a hunch.

Slide 23 – looking at specific comparative evidence most trials found no difference. And I'm just going to highlight the four trials that did find differences with one drug compared to another. For instance, two trials reported higher incidents of sore throat for fluticasone compared to beclomethasone. One trial reported a higher incidence of oral candidiasis for fluticasone compared to triamcinolone and one trial reported more upper respiratory tract infections for triamcinolone compared to beclomethasone. And again that just focuses on those trials that did find significant differences.

Slide 24 we added a couple of studies here looking at bone density or osteoporosis and we really…what we were looking for were studies that addressed fractures as the final outcome here with bone mineral density being an intermediate marker of risk for fracture. So the first group of studies that I'll review do address fracture. There were three observational studies that suggested an increased risk and that was countered by two randomized trials and one observational study that did not find an increased risk and subsequently the evidence for bone mineral density also was mixed. There was one randomized trial and one observational study that found a reduction in bone mineral density especially at higher doses and again then four randomized trials that did not find a reduction. So we deemed this evidence to be insufficient to draw conclusions about one drug compared to another or for that matter difficult to draw conclusions as to whether or not any of these drugs really significantly effect the risk of fractures.

Looking again at growth retardation on slide 25. There were two head-to-head trials that looked at short-term growth and we characterized this as less than one year and found that growth was significantly less reduced with fluticasone than with beclomethasone and budesonide. However, looking at some of the placebo-controlled evidence most of the placebo-controlled studies report significant reduction in growth over one to four years compared to placebo, but the question is whether or not that translates into long-term reductions in growth. The only evidence that we have comes from a long-term study, which was 9.2 years that found no differences in adult height for budesonide compared to placebo, which sort of makes it difficult to know how comparative evidence might compare if you were to extend the duration of these studies. So we rated the overall grade of this evidence as fair to poor.

We didn't find any new evidence for acute adrenal crisis, cataracts, ocular hypertension or glaucoma or sub groups—race, age, gender, co-morbidities. You have those slides. So I'm happy to cover them if you want, but I'm going to skip through them for now and move on to slide 34, which is a summary slide. So just to summarize everything then there's inconsistent evidence from narrowly defined asthmatic populations. In other words, mostly representing randomized controlled trials with relatively strict inclusion criteria, exclusion criteria that support only minor differences between inhaled corticosteroids and that's only on some health outcome measures like I demonstrated with beta-agonist issues and asthma symptoms.

Slide 35 there's insufficient evidence to draw conclusions about the comparative effectiveness or efficacy of inhaled steroids for COPD.

And slide 36 fair evidence exists for that overall tolerability does not differ substantially. We did feel that the evidence that compared budesonide and beclomethasone to fluticasone needed to be highlighted. That that reduction in short-term growth could be clinically important and that…however, fair to poor evidence is inconclusive with regard to how that translates into long-term growth reduction and for that matter risk of bone fractures, acute adrenal crisis, cataracts and glaucoma.

Slide 37 gets back to this device and dosing issue and this highlights our conclusions from the addendum of the report. Really the existing evidence didn't clearly identify one device or dosing regiment to be superior with regard to efficacy or tolerability. We did find some evidence that twice daily dosing is more efficacious than once daily dosing in patients with more severe disease although from this evidence base it appeared that patients with mild to moderate disease can be effectively managed on a once daily dosing regiment and the evidence with regard to…with device and dosing regiment and adherence really what that suggests is that it may be driven more by patient preferences for that treatment or their ability to use a particular device more so than the actual efficacy of a device in improving outcomes. So that evidence from what we found there's really no consistent direction in the nature of that relationship. And that's all I had unless…I'm happy to take any questions that you have.

Dan Lessler: Thanks, Rick, that was really an excellent summary and presentation. Actually, what I'd like to do is if you can stay on the line that would be helpful. What we normally do here is…I was just going to open it up to questions to you from P&T Committee members for clarification and then following that we allow time for stakeholder input. And if it's possible for you to stay on the line through the stakeholder input that's helpful because sometimes there are questions that arise in the context of comments of stakeholders.

Rick Hanson: Sure. One request from my end for some reason the voice seems to break up a little bit. I don't know if that's a function of where the microphone is.

Dan Lessler: I don't know. Can you hear me better now?

Rick Hanson: Much better.

Dan Lessler: All right. It's just this microphone sort of goes in and out. So…okay, so first Rick, I was just going to ask if there are members of the committee that had questions for you…questions from the committee about Rick's presentation? Points of clarification and such? No? Okay. So we're going to open it up to stakeholder input and I've got…I have three people who are signed up. If you are planning to comment…has everybody who is planning to provide comments signed in? Okay. Then first is Dr. Legg. And I would ask if people could please identify yourself and if you're…who you're representing and if you are not associated with a company if you have any sponsorship, as well I ask the people please limit their comments to three minutes. Thanks.

Randy Legg: Okay. This is Randy Legg. I'm a PharmD from Astra Zeneca. I work in the respiratory medical affairs side. I'd like to comment on the growth studies. The short-term growth reduction that was mentioned by Dr. Hanson was a short-term phenomenon that is seen almost all steroids. What happens is after the first year growth catches up and then I'd like to highlight the long-term study of 9.2 years where it showed that the patients on Pulmicort achieved normal adult height compared to placebo. That's pretty consistent across all inhaled steroids.

Another comment I have is budesonide is the only category B pregnancy safety-rating steroid of all the inhaled steroids available. And number two is Pulmicort respules is the only nebulized corticosteroid age 12 months to 8 years of age. And that's it unless you have any questions for me on behalf of budesonide.

Dan Lessler: Nothing. Thank you.

Randy Legg: I promised to be brief. So.

Dan Lessler: I appreciate it. Next is Dr. Zarling(?).

Meredith Zarling: Good morning and thank you for the opportunity to present information of on Flovent. My name is Meredith Zarling and I'm a pharmacist and a regional medical scientist with GlaxoSmithKline. I would like to present information in support of Flovent on the preferred drug list. According to the American Lung Association of Washington, Washington state's asthma prevalence has been identified by the CDC as one of the highest in the nation. More than 5,000 people are hospitalized every year as a direct result of asthma and more than half of the hospitalizations are paid for by Medicare or Medicaid.

First I'd like to highlight a point from the Oregon EPC Drug Class Review on inhaled corticosteroids. The review noted that the number of puffs for some products to reach equipotent doses could be substantial where a medium to high dose of inhaled corticosteroids are needed to provide asthma control there are higher strengths of Flovent available. This would allow most patients to use two puffs per dose or a maximum of four puffs per day to maintain control of their asthma. In a Cochran collaboration review from 2005 it was concluded that most patients with mild to moderate asthma experienced similar results with lower doses compared to higher doses of fluticasone. The use of the lower dose may optimize the risk benefit ratio and provide cost savings.

A retrospective analysis of health plan data was used to assess the low dose approach. One study compared the monthly cost of fluticasone at the low strength to other inhaled corticosteroids. A total of 1,956 patients were included in this study. Results determined that annual asthma care charges, pharmacy and medical over the 12-month observation period were significantly higher in patients treated with beclomethasone, triamcinolone, budesonide and flunisolide compared to fluticasone. In addition, patients treated with beclomethasone, triamcinolone and flunisolide were associated with significantly higher total health care, asthma and non-asthma charges compared to patients on fluticasone.

In adult asthma patients in randomized double blind studies fluticasone demonstrated similar to significantly less suppressive effects in the HPA access compared to beclomethasone or triamcinolone at therapeutically equivalent doses.

In summary, there is some comparative clinical evidence favoring fluticasone as evidenced in the EPC drug class review in inhaled corticosteroids. There are three available strengths of Flovent, which provides an effective way to deliver the needed dose with a reasonable amount of puffs.

Finally, there is a database analysis, which suggested the asthma care and total health care costs may be lower for patients filling Flovent low strength prescriptions compared to patients filling prescriptions for other inhaled corticosteroids. Based on this information, the Medicaid population would be best served if fluticasone were available on the preferred drug list for the state of Washington. Thank you very much for your time.

Dan Lessler: Any questions for Dr. Zarling from…? Okay, thank you. Next is Dr. Manning.

Dan Manning: Good morning. My name is Dan Manning and I'm a medical science specialist with Shearing Ploughs Global Medical Affairs and I'm here to talk about Nasonex twist haler, which is mometasone. I just want to make a few comments on that. It's the only FDA approved ICS approved for once daily administration at initiation and for maintenance treatment of asthmatic patients.

In clinical trials it's shown to be very safe and effective. It has a total systemic bioavailability of less than 1%. At the recommended FDA doses no HPA access suppression was seen. One of the advances with the Nasonex device is that it is a dry powder inhaler. So you don't have to coordinate actuation with inhalation, which makes it easier for the patient. Also it has a dose counter on it, which allows the patient to know how many doses they have on. And really in conclusion I just want to make a comment that Nasonex has been shown to be safe and effective and it's the only

FDA approved ICS indicator for once daily administration at initiation and for maintenance treatment. Thank you.

Dan Lessler: Thank you. Any questions? All right. It seems like there aren't any questions that the committee members have then that we would want to have Rick Hanson's advice on. Rick, I think we can let you go here.

Rick Hanson: Okay. Well, if anything comes up feel free to give me a call. I'll be here until 1:00 if you need me.

Dan Lessler: Great. Well, that's very kind of you. Thanks a lot and thanks for your presentation.

Rick Hanson: You're welcome. Bye.

Dan Lessler: I think maybe the place to begin here is if people could…on the committee could just turn to the last motion that was adopted by this group and maybe we could start there and I would ask based on the presentation we just heard if…just what people's thinking is relative to that prior motion that currently stands and people have any particular comments.

Bob Bray: This is Bob Bray. Is this on? The comment I have is really a question. Our statement talked about having a pediatric formulation. So given the variety of information that we've had with pediatric side effects and so forth, my question is what is being considered for a pediatric formulation because the age ranges with the FDA have attached to these are not necessarily going to follow what physicians are doing, I think? So do we have anybody who can tell us that? What products were considered pediatric?

Dan Lessler: Donna?

Donna Sullivan: This is Donna Sullivan. I think the Pulmicort respules are preferred for pediatric…the population less than…I forget the actual age, but they are the ones that are used in the nebulizers.

Bob Bray: So then that's the only drug that's considered a pediatric product according to how we've listed our proposal?

Siri Childs: This is Siri Childs and I don't have it on the top of my head, but I know last year when we evaluated this given your recommendation we were sure that we had all pediatric ages covered with the products that we put on the list. So I think an open statement regarding pediatric formulations will serve us well again this year.

Bob Bray: One of the things that came to mind hearing this with the information is that at least short-term fluticasone looked like it had some advantage over two other products regarding the rate of growth reduction, but fluticasone is not going to be identified then as a pediatric product. And I guess I'm just wondering if somebody, you know, if a parent is looking at the Internet and coming up with that information and it's not available as a pediatric product that could be a problem.

Jeff Graham: This is Jeff Graham. If you look at our current preferred drug list fluticasone is on the preferred drug list.

Bob Bray: They are all on the preferred drug list, but that could change pending…not necessarily what we change, but that could change based on bid information and so on. Correct?

Jeff Graham: Well, it could, yes, but if you direct us for the pediatric preparation that we would probably do the same as we've done in the past.

Dan Lessler: I think Bob…

Bob Bray: Do you see the potential issue?

Dan Lessler: Bob's point is that fluticasone might not necessarily be included because it's not FDA indicated.

Bob Bray: It looks like it's not going to be identified as a pediatric product.

Janet Kelly: This is Janet Kelly. If we look at this the way we worded it though we said that it had to conclude a product that was high potency with four puffs per day or less. So if the provider wants to use that it doesn't matter whether they are pediatric or not. We specified in this motion here that we have to have that one on. We haven't specified it for pediatrics, but we've given the option for a high potency.

T. Vyn Reese: Hi, this is Dr. Reese and this is a category we've already reviewed. I think that we already have a really good motion already done. My only slight modification would be there are high potency products now that have six puffs per day instead of four. I think that's a small difference and I think we could maybe change it to six puffs a day instead of four, but I don't see anything else wrong with the motion. I think the motion really covers most of the important issues and not a lot of new material has been presented to the committee since our last discussion on this group. So I would basically just…that would be the only thing I would change—I would change it from six puffs instead of four and leave everything else the same if it were my motion to make.

Dan Lessler: Right.

Patti Varley: This is Patti Varley. Don't we have to add the new one because there's no evidence.

Dan Lessler: Right. We would add mometasone, yeah.

Jason Iltz: This is Jason Iltz. The only other comment I would make in terms of changes potentially to a new motion would be mometasone is not currently at least on the NAEPP guideline for interchange. So we may want to also add the additional IPAG, the International Primary Care Airways Group recommendations because that was is on if we want to maintain this particular class as being interchangeable. The other thing that I would bring up and being a pharmacist that I think pharmacists clearly can certainly interchange these if the appropriate information is available, but the other portion that needs to be considered is device and delivery and there is a whole host of different types of devices and delivery systems that are out there. So it's more than just interchanging between an equipotent dosage. You also have to make sure that the patient can manipulate the inhaler that you're switching them to. So I guess that just opens up the discussion for should this class be therapeutically interchanged due to those considerations because it's more than just dosage equivalency issues and then to your other point we do need to add mometasone up to the drug list as well.

Bob Bray: This is Bob Bray. I guess the concern about Vyn's suggestion about allowing high potency products go up to six puffs would then potentially negate the presence of fluticasone on the list since that's…that's the other reason why the pediatric product wasn't necessarily important by Janet's comments is that it would include fluticasone because of the four puffs per day limit.

Dan Lessler: My concern was to be more inclusive to include other possibilities to have in the formulary not saying that fluticasone would need to be the only high potency steroid. I think the evidence is poor as to the differences. There is some evidence that shows fluticasone is more irritating and there's one study or so that shows there is a short-term growth deficit in children, but then long-term it doesn't look like there is any. So it's very confusing to me and, you know, I think we should be more broadly inclusive. Six puffs versus four is I mean there are lots of other ones now that are less than four. Mometasone now is down to two puffs a day for a high dose. So it doesn't mean that fluticasone would have to be one it because it's less than four. There are other drugs that certainly get their less than four doses.

Bob Bray: Bob Bray again, I guess we're sort of mixing some of the issues between adult and pediatrics. From my perspective, from a pediatric perspective, I think that since there at least is some information that short-term favors fluticasone over two other products for children whatever it is that we do I think we should make sure that fluticasone, however we word it or however we craft I think fluticasone from a pediatric perspective needs to be there. From the adult perspective I agree, I don't think that there is reasons why that should stand out from the adult perspective. From a pediatric perspective there's at least one reason why I think it should be available.

Jason Iltz: This is Jason Iltz again. If I remember to our discussion, which was a little while ago, but the conversation we had in relation to a pediatric product was trying to cover the most patients through the FDA approved route. So there is really only one product that goes down to 12 months of age and then the other consideration was that product also was pregnancy category B and it was in a formulation that allowed to give down to that particular age group because it was nebulized. So for the fluticasone we still have some of the delivery issues potentially with some of those younger pediatric populations.

Dan Lessler: Yeah, I think Bob would acknowledge that. So, you know, it sounds like what we're…where we're headed is maybe just specifying that at a minimum budesonide and fluticasone need to be available and then, you know, beyond that I think maybe this motion could stand as I think about it. How does that sound to people in terms of where the discussion is going here? [end of Side A]

[Side B]

Carol Cordy: Are we saying to include both the nebulized form and the DPI, which I think is not on the preferred drug list right now?

Dan Lessler: Are they both available?

Man: Just the nebulizer.

Carol Cordy: So we would have to add the DPI of the budesonide, as well.

Man: To cover the pregnancy?

Carol Cordy: To cover the pregnancy, yeah.

Dan Lessler: So it sounds like in terms of the actual preparation and that piece and dosing we can…we're sort of headed towards a minor modification of the existing motion. I just wanted to come back to Jason's point around the device and see if people had comments or thoughts about that that had to do with interchangeability so that, you know, two preparations might be interchangeable in terms of dose, but how it's actually delivered whether or not there is something more we want to call out in terms of a motion there. Or should we just leave it?

Bob Bray: I think I would just…the devices are becoming so diverse and the number of different delivery systems is so complex that it is very difficult to therapeutically interchange them, but I don't know if we want to get into that fine of a discussion. It's…the provider has to judge that and order it as, "Dispense as written." If they find that there is a problem, you know, if for some reason somebody mechanically can't handle one device and they can another then the provider would know that individual case better and be able to decide that and prescribe it that way. That would be my point. I think we have to leave some of this to the discretion of the provider.

Dan Lessler: Sounds like…Jason, you're okay with that?

Jason Iltz: This is Jason. I like that rationale.

Dan Lessler: Okay. So at this point I think we're pretty close to just a modification of this motion. I don't know if somebody would like to take a try at that?

Carol Cordy: I just want to make one more comment. I agree in a sense to have it be the prescriber's decision, but in reality what happens is if something is not on the preferred…is not a preferred drug on the list…on the preferred drug list patients actually don't get it. I mean they would not get the…say on the budesonide the DPI if that were not…if that were prior authorization as it is now people maybe don't get it. It's a hassle in practice for prescribers to know how to get around that.

Jeff Graham: This is Jeff Graham. All they have to write is dispense as written. There's no pre-authorization otherwise. If they dispense as written that's what they get. Because this class is on our preferred

drug list so there is no prior authorization for this drug unless a person is not an endorsing practitioner.

Carol Cordy: Okay. It was not…at least when I looked it up it was not on the list. That was my question.

Dan Lessler: The budesonide, the DPI?

Carol Cordy: Right.

Dan Lessler: Well, we're going to change the motion. We're going to change this to specify that it should be. I think that's the plan.

Carol Cordy: That's going to be a specific change?

Dan Lessler: That's the intent here. So would somebody like to try putting forth the motion just with appropriate modifications based on our discussion here?

T. Vyn Reese: So the committee will have to help me if I leave anything out since we modified this a little bit. This is Dr. Reese. Um, after considering the evidence of safety, efficacy and special populations for the treatment of asthma, I move that beclomethasone dipropionate, budesonide – both DPI and nebulization, flunisolide, fluticasone, triamcinolone and mometasone are safe and efficacious. Budesonide must be on the formulary for pregnant patients.

A pediatric product; a high potency product, which can be administered in six puffs per day or less; and a breath-activated device must be included on the Washington Preferred Drug List.

For the treatment of asthma on the Washington Preferred Drug List the inhaled corticosteroids can be subject to therapeutic interchange using resources such as the National Asthma Education and Prevention Program expert panel and the International Primary Care Airways Group, as long as the above concerns are addressed.

Dan Lessler: Can I make a friendly…I think it might…Carol might feel more comfortable if we said budesonide and actually specified that, you know, DPI and nebulizer…

Woman: Did you say that that was for a particular indication? I think I'm…for pregnancy?

Dan Lessler: Yeah, Bob.

Bob Bray: This is Bob Bray. I think we talked about stipulating that both budesonide and fluticasone should be added. If we did not for pregnancy obviously it wouldn't be for that indication. If we did that then you could eliminate the paragraph that starts the pediatric product because we've covered that with that stipulation of those two drugs.

T. Vyn Reese: This is Dr. Reese. Does fluticasone have a pediatric…it doesn't have a pediatric formulation? It's greater than 12 years so we can't do that.

Woman: No, it's 4 to 11 years. It has been approved for 4 to 11 years.

Bob Bray: If there's been a prior treatment then it is…

T. Vyn Reese: It's okay from 4 to 11, but not the very young children? They would have to go to the budesonide, which is…

Bob Bray: Inhaled, which is…

T. Vyn Reese: So how do you want to put that in there, Bob?

Bob Bray: So I would suggest before budesonide just put fluticasone must be included on the preferred drug list.

Woman: Doesn't budesonide have to be included? Why do we have to say pregnancy? It's like it needs to be included on this list.

Dan Lessler: Okay. So it's there. And then I think that paragraph right where you're blinking…we'll come back down. A pediatric product, a high potency product, which can be administered. The rest of that can be deleted because we've covered it.

Carol Cordy: Carol Cordy, again. The way this is written would there be any chance that I would write for one and it might be exchanged when I don't intend for it to be exchanged? If I'm writing for budesonide for a pregnant patient could that be interchanged by the pharmacist?

Donna Sullivan: This is Donna Sullivan. No, we don't exchange preferred drugs. We only exchange non-preferred drugs.

Carol Cordy: Okay.

Donna Sullivan: So if you write for a preferred drug we would never switch it to something else. It would automatically get filled.

Dan Lessler: Donna, the…second down last paragraph International Primary Care Airways Group should be capitalized. And then I guess…what's the acronym?

Man: IPAG.

Dan Lessler: IPAG sort of in parenthesis after that is the abbreviation.

Man: And for clarification we may want to say and/or after the two different types of [inaudible].

Dan Lessler: Right. Right.

Man: [inaudible] and/or.

Jeff Graham: Do the and/or between NAEPP and…

Dan Lessler: All right. So could you scroll back to the top and maybe I'll just read this here again and we can…so, after reviewing the…maybe I'll…

T. Vyn Reese: It's my motion. I started it out as my motion, but it's been helpfully modified by other committee members. So thank you. So after reviewing the updated information on inhaled corticosteroids, I move that beclomethasone dipropionate, budesonide, flunisolide, fluticasone, triamcinolone and mometasone are safe and effective for the treatment of asthma. Fluticasone and budesonide a DPI nebulizer must be on the Preferred Drug List. For the treatment of asthma on the Washington Preferred Drug List, the inhaled corticosteroids can be subject to therapeutic interchange using resources such as the National Asthma Education and Prevention Program, the NAEPP expert panel report and/or the International Primary Care Airways Group as long as the above concerns are addressed. That's the motion.

Dan Lessler: All right. Excuse me just for a moment. Is that Susan Carson?

Susan Carson: Yes, it is. Hi.

Dan Lessler: Hi, Susan, it's Dan Lessler. We're just finishing up with the inhaled corticosteroids. We'll be with you in just a minute here.

Susan Carson: Okay. Thanks.

Dan Lessler: Okay, thanks. Are there other…

Carol Cordy: Effective is not the word we want to use. We want to use efficacious in the first…they were efficacy studies not effectiveness.

Dan Lessler: Okay. All right. So there's the motion on the…is there a second?

Kenneth Wiscomb: I'll second it with the minor changes of the way it reads. Fluticasone is available by nebulizer and I don't believe it is. We need to specify the delivery method for fluticasone in parenthesis and then put a parenthesis around DPI and nebulizer for budesonide.

Dan Lessler: Okay. There we go.

Kenneth Wiscomb: But I'll second the motion.

Dan Lessler: Okay. Fluticasone comes in a rotor disk too. It's not just an MDI so you can't…I think we have…if we just have the fluticasone and then budesonide with the parenthesis I think we're fine. So are you…can we take that as a second? Great, thank you. So why don't we go ahead and go ahead and vote at this point. All those in favors please say, "I."

[committee] I.

Dan Lessler: Opposed, same sign? All right. Great. Well, we're right on time for our second drug class review, which is an update on the non-sedating antihistamines. So Susan we're just…give us a second here. We're just teeing up your PowerPoint presentation and I'll let you know when we've got it up here in just a second.

Susan Carson: Okay.

Duane Thurman: Excuse me. This is Duane. I just want to clarify, are the mikes on and then you're controlling the volume? So all we have to do is…just so we don't have to keep messing around with the mikes. Thanks.

Dan Lessler: Yeah. Okay, Susan, we have the PowerPoint projected and we're looking at your title slide and you can take it from there and tell us when you want to change slides.

Susan Carson: Okay, great. So I just want to let you know that I'm presenting this update on behalf of Susan Norris who is the principal investigator, but she was not able to be here today. Next slide shows that drugs that we included in the review – cetirizine, desloratadine, fexofenadine and loratadine. No new drugs were added this update.

Next slide shows key question one about effectiveness and efficacy. There were three changes to the scope of the report for this update. They were made at the request of participating organizations of DERP and they were that we included children this update, as well as updates. We also included all types of urticaria not just chronic idiopathic urticaria as in the original report. And then we also included studies of any duration rather than limiting them to studies of 14 days or longer as we did in the original report. So I'll be presenting the updated information for adults and all the information in children is new that I'll be presenting.

Next slide titled search strategy – for adults we searched from the end date of the last search through August 2005 and for evidence in children we searched all literature up to August 2005.

Next slide shows the search results for the update. We identified 352 new studies in our updated search and we also went back over our existing library of studies to search for studies in children and for trials less than 14 days duration. So for adults we added 22 studies to the original 27 that were included. For children 29 studies met our inclusion criteria and we also identified 11 trials of less than 14 days duration.

Next slide – seasonal allergic rhinitis in adults. There were no new head-to-head trials included this update. We identified one, but it was rated poor quality so it's not considered in the assessment of the evidence. There is still no head-to-head comparisons of desloratadine to other antihistamines in

adults with seasonal allergic rhinitis. A new placebo-controlled trial found fexofenadine improved quality of life, work productivity and total symptom score compared to placebo. And we identified new active control trials, but they did not add comparative evidence.

Next slide – perennial allergic rhinitis in adults. No new trials in adults were identified for this indication so still no head-to-head evidence. One systematic review was included. It included all antihistamines including first generation and the newer drugs and it concluded that oral antihistamines produce significant improvements in-patient and health care worker assessed symptoms versus placebo, but the review didn't look at comparative evidence. One new placebo-controlled trial found desloratadine was more effective than placebo in 12-hour total symptom score.

The next slide – this summarizes the evidence for studies with less than 14 days of follow up. These are new this update. So these studies assessed responds after either a single dose, two days or three doses. So they were very short term. And they were all conducted in patients with either a seasonal allergic rhinitis or they didn't specify the type of allergic rhinitis. There were no studies in perennial allergic rhinitis or urticaria. In studies conducted in an environmental exposure unit cetirizine was better than loratadine and fexofenadine for a total symptom score, but time to onset was similar. In one study cetirizine was similar to loratadine for symptoms control, but cetirizine had a faster onset of action. Two studies were conducted in park settings during the allergy season and in these cetirizine was better than loratadine in one of the studies and fexofenadine reduced symptoms more than placebo in the other. So to summarize as a group the studies provide evidence that cetirizine, loratadine and fexofenadine decreased symptoms after one or two doses. Cetirizine was better in some studies, but there was conflicting evidence depending on the outcome and throughout the different studies. Also we want to point out that the generalizability of these studies is limited.

Next slide – chronic idiopathic urticaria in adults. Well, actually it should be titled just urticaria in adults. And we identified one new head-to-head trial of cetirizine versus fexofenadine for chronic idiopathic urticaria. And no comparisons of desloratadine to other antihistamines.

The next slide – the new head-to-head study Handa 2004 compared cetirizine 10 mg to fexofenadine 180 mg for 28 days of follow-up. Cetirizine was more efficacious than fexofenadine for total symptom score. This study was limited by a high drop out rate. Also a new placebo-controlled trial found fexofenadine significantly more efficacious than placebo and there's still no comparative evidence in urticaria for fexofenadine versus loratadine or for desloratadine versus other newer antihistamines.

The next slide, slide 11 we included no studies of other types of urticaria in adults. We did identify studies but they were rated poor quality and not considered in the assessment of the evidence.

Okay. The next slide. We're moving onto the evidence in children. So this is all new for the update. It's a new population. For seasonal allergic rhinitis in children we identified 10 studies and two of these were rated poor quality and there were no head-to-head studies.

The next slide placebo-controlled trials of cetirizine and fexofenadine showed significant improvement for the active drug compared to placebo. The only placebo-controlled trial of loratadine that we identified was rated poor quality. That was Bender 2004.

The next slide. We identified four active controlled trials of seasonal allergic rhinitis in children. One of these was rated poor quality and the active control trials found no differences for loratadine and cetirizine compared to first generation drugs.

Next slide – perennial allergic rhinitis in children. We identified eight studies in children and one of these was rated poor quality.

Next slide. All but one of the studies for perennial allergic rhinitis in children studied cetirizine. There was one placebo-controlled study of loratadine. Most of these trials included children ages 6

to 12 or 6 to 14. One was conducted in children ages 2 to 6. That was the head-to-head trial. And the head-to-head trial looked at loratadine versus cetirizine.

Next side. This summarizes that head-to-head trial of cetirizine versus loratadine. In this study of 80 children ages 2 to 6 the primary efficacy outcome was inhibition of the will response at the end of 28 days of treatment. Symptoms were also assessed by parent's daily and by investigators at the end of the treatment. So on the primary outcomes cetirizine produced greater inhibition of will response than loratadine and on the secondary outcome of global assessment of symptoms by the investigator symptoms decreased in both groups and there was…but there was no significant difference between the two groups. On symptoms assessed by the parents, parents reported that both drugs produced substantial relief, but cetirizine was more effective than loratadine for nasal symptoms.

Next slide. In three active controlled trials in children with perennial allergic rhinitis cetirizine was better than the comparator. In placebo-controlled trials that are shown back on slide 16 cetirizine and loratadine were more effective than placebo in this group of children. And there was no data for fexofenadine or desloratadine in children.

Next slide – urticaria in children. There are no head-to-head trials of newer antihistamines for this indication in children. There were two studies of cetirizine—one active and one placebo-controlled. In the active controlled study there is no difference between cetirizine and oxatomide although there was a reduction in symptoms in both groups after four weeks of follow-up. And in the placebo-controlled trial cetirizine was more effective than placebo for prevention of acute urticaria in young children with atopic dermatitis. And there are no data for other drugs in these children.

Next slide – key question 2 addressed safety. So for the update information we can skip over to slide 25, which shows adverse events in adults for update 1. Eleven new studies provided information about adverse events in adults. Headache was the most frequent adverse event and rates of withdrawals due to adverse events were low and serious adverse events were rare. In the head-to-head study cetirizine was similar to fexofenadine for drowsiness, constipation, abdominal pain, epigastric pain and cough.

Next slide. QT interval was measured and reported in three new studies in adults. In two active control studies with loratadine there was no difference between loratadine and the comparator in the QT interval. Prolongations in QT interval were mild and they occurred in 1.6% to 3.6% of patients. And that was not significantly different from placebo or the active comparator. And in a study of fexofenadine versus placebo they reported no clinically relevant ECG changes.

The next slide shows adverse events in children. Adverse events were examined in 17 efficacy studies and in 5 other additional observational studies. This slide summarizes their percentage of specific adverse events such as headache, insomnia, nervousness found in the studies. The numbers in the parenthesis are either placebo or the active comparator. So they were similar between the…the rates were similar between the newer antihistamine and the comparator groups. In the head-to-head trial of cetirizine versus loratadine there was one…and that was in 80 patients. There was one patient with generalized rash and one with somnolence and both of these were in the cetirizine group and the patients withdrew because of these adverse events in both of those cases. And there were no withdrawals due to adverse events in the loratadine group.

Next slide. Five studies of cetirizine and fexofenadine…well, four of cetirizine and one of fexofenadine looked at QT interval in children and none demonstrated a significant prolongation in the QT interval.

Next slide. This summarizes results…adverse events for the early treatment of the atopic child trial, the ETAC trial. Now we didn't include this for efficacy because the population was…it didn't meet our inclusion criteria, but we did include it for safety because it's the longest term study of cetirizine in young children. So it provided good evidence about adverse events. And in this trial serious adverse events were actually less common with cetirizine than with placebo and there was no difference in hospitalization rates between the groups, no differences between the groups in ECG changes and no prolongations of the QT interval.

Next slide. Key question 3 addressed the comparative evidence in subgroups based on demographics, other medications or co-morbidities.

Next slide, slide 31. New evidence in subgroups for the update was consistent with existing evidence and it does not change the conclusion that there is no direct evidence that any newer antihistamine has an advantage in efficacy for any subgroup based on race or age or other factors.

Next slide. This is about pregnancy. The existing evidence. We can skip to the next slide for the new evidence in pregnancy, slide 33. So we included one new observational study of the use of antihistamines in pregnancy. This was the National Birth Defects Prevention Study and they found that there was no relationship between loratadine use in pregnancy and hypospadius in infants.

The next slide. This summarizes the new evidence in adults for update one and if you have it available I'll refer you to the conclusions, which are shown in Table 18 of the updated report. That's on page 35. So to summarize for seasonal allergic rhinitis and perennial allergic rhinitis in adults the conclusions do not change. There is limited new evidence that suggests that for chronic idiopathic urticaria cetirizine may be more efficacious than fexofenadine. New evidence from studies of one or two doses also suggests that cetirizine may also be more efficacious than fexofenadine for seasonal allergic rhinitis symptoms. The evidence for cetirizine versus loratadine in these very short term studies was mixed. Also limited evidence suggests that there is no prolongation of the QT interval with loratadine and fexofenadine.

The next slide summarizes the new evidence in children for seasonal allergic rhinitis and urticaria there are no data based on direct comparisons for comparative efficacy. For perennial allergic rhinitis one small fair quality study suggests that cetirizine may be more efficacious than loratadine, but there is insufficient evidence for other comparisons. There is also insufficient evidence about comparative safety in children. There's fair quality evidence on the safety of cetirizine and loratadine and limited evidence on the safety and desloratadine and fexofenadine in children. And that concludes the update.

Dan Lessler: Great. Thank you. Susan, I was just going to open it up for questions to you from P&T Committee Members if there were any points of clarification. I may ask if any members have questions for Susan.

T. Vyn Reese: Susan, this is Dr. Reese. I have questions about cetirizine sedation effects. Cetirizine has a warning in the PR about not driving while using cetirizine. In these studies the sedation doesn't seem to be that much different than the other non-sedating antihistamines. Do you want to comment on that? How much evidence is there to cetirizine sedative effects?

Susan Carson: I'm sorry. I couldn't hear…I could only hear the very first part of that question, which was a question about evidence for…or that there was a warning for driving while taking cetirizine. And I couldn't hear the rest of it.

T. Vyn Reese: This is Dr. Reese again. There is a warning in the PR about driving with cetirizine and its sedative effects about…that is a contraindication. I want you to comment on that and the evidence that has been presented on cetirizine's sedation compared to the other "non-sedating" antihistamines.

Susan Carson: Right. Well, um, for the new evidence we actually…there was a study, um…a simulated performance measure…oh, actually, that was fexofenadine so that wouldn't work. That wouldn't answer your question. Um, let's see. Well, what we found in this update a cohort study and two small RCTs found loratadine less sedating than cetirizine and again three RCTs did find cetirizine more sedating than fexofenadine. So I'm looking at our summary of the evidence table and it says cetirizine is more sedating than cetirizine. So that's probably an error and it should say cetirizine is more sedating than loratadine and fexofenadine.

Dan Lessler: Thanks for that clarification, Susan. Are there any other…Ken?

Kenneth Wiscomb: Have there been any concurrent studies looking at the concurrent use of fexofenadine and erythromycin in terms of effect on the QT prolongation?

Susan Carson: Could you repeat the question, please? It's difficult for me to hear.

Kenneth Wiscomb: I'm sorry. There was a slide that looked at one agent taken concurrently with erythromycin looking at the prolongation of QT interval and I was just curious about whether or not a study had ever looked at the concurrent use of fexofenadine and erythromycin in that regard?

Susan Carson: We didn't find any evidence about that. Just the one study, which I didn't mention. It was a poor quality study, which found no prolongation of the QT interval with cetirizine or loratadine in children who are also taking erythromycin.

Kenneth Wiscomb: Thank you.

Dan Lessler: Are there other points of clarification here? Okay. We were going to open it up for stakeholder input and Susan if you can just stay on the phone a few more minutes here actually I think I just have one person signed up and that's Dr. Manning.

Dan Manning: I'm Dan Manning with Shearing Ploughs Global Medical Affairs, again and I just want to talk about Clarinex or desloratadine. As we know it's a long-acting, non-sedating antihistamine. It's the only non-sedating prescription antihistamine for PAR and the only non-sedating prescription antihistamine approved for once daily treatment of CIU. One of the big advantages of it, obviously is it's non-sedating and you can take it while operating machinery or driving and one of the questions that came up in the last few minutes here was that desloratadine is well tolerated and it has not been associated with clinical relevant drug interactions when it is administered with drugs such as erythromycin, ketoconazal and fluoxetine. So I just wanted to make that clear. And it's available down to…or indicated down to six months of age for patients with PAR and also has several dosage forms including a tablets, reditabs and syrup formulation. Thank you.

Dan Lessler: Thank you. If there aren't any other questions for Susan I think we can let Susan…Susan, I think we're all set. I appreciate your presentation and comments and we can let you go here.

Susan Carson: Great, thanks.

Dan Lessler: Thank you.

Susan Carson: Bye, bye.

Dan Lessler: So, um, again this is an update from previous presentations and there is a standing motion that was adopted last time. Maybe we could just…it looks like everybody is taking a look at that. And again as with the inhaled corticosteroids I thought we could begin just by people could take a look at this and based on the update I'm wondering if there are any comments on the existing motion and people's feelings about making any modifications to it or the need for any modifications.

Carol Cordy: Carol Cordy here. I wanted to bring up again just the definition of non-sedating versus sedating because I think in the literature and certainly on the…in the [inaudible] the…cetirizine is not listed as a non-sedating antihistamine. Are we changing the definition?

Dan Lessler: Do you want to comment?

Donna Sullivan: This is Donna Sullivan. We could change the name from non-sedating to second generation. Is that appropriate?

Man: If you would look at the presentation it says newer antihistamines and that's actually how Oregon now…or the EPC classifies this group is newer antihistamines.

Dan Lessler: So could we then…that's a good point. Can we then make that change in terms of the title of the motion as well?

Patti Varley: This is Patti Varley and this is just memory clarification from when we did this. Does somebody remember the rationale for should contain loratadine?

Bob Bray: This is Bob Bray. I believe the issue was the pregnancy category B. We have two choices that are pregnancy category B, but I think that was what the rationale was.

Patti Varley: Would it be more feasible then to say it must include a category B agent as opposed to listing a specific agent?

T. Vyn Reese: As we just previously mentioned cetirizine isn't non-sedating so we wanted to be sure that loratadine is on the list because it is category B and it is non-sedating. I think that was the way we looked at it before. That's how it ended up there. I had one question, loratadine is OTC. Is it still provided for medicating patients or how does that work?

Siri Childs: Yes, this is Siri Childs. Speaking for Medicaid OTC loratadine is our preferred drug and we cover it.

T. Vyn Reese: Thanks.

Dan Lessler: Bob?

Bob Bray: I'm going to be on the pediatric scene today, I guess. There are some differences in those groups between how young they're indicated for children. For instance, fexofenadine has an indication, but doesn't have a syrup formulation. Is that correct? And loratadine is indicated only, I believe, down to age two. So if we added in there that there must be a pediatric formulation down to six months of age that would get us covered with the pediatric formulation.

Dan Lessler: Okay. So other comments in terms of modifications?

T. Vyn Reese: We still need to modify non-sedating. We just could say newer antihistamines although it would make it consistent all the way through. But non-sedating is sort of listed again about two-thirds of the way through the motion and just change it to newer.

Dan Lessler: So from what I've heard so far is that potentially modifying the existing motion and rather than specifying loratadine we would specify category B non-sedating and the availability of a form that's FDA approved down to six months of age? Jason?

Jason Iltz: This is Jason. Siri, the question for you to the OTC loratadine, are all dosage formulations covered including reditabs, the liquid, because all of those are available?

Siri Childs: Right.

Jason Iltz: Okay.

Dan Lessler: Any other comments at this point? Jason, looks like…

T. Vyn Reese: It should be non-sedating in pregnancy. Right? There's only one drug in the category—loratadine is the only one that's non-sedating and also a category B in pregnancy.

Dan Lessler: Jason?

Jason Iltz: This is Jason. So mechanistically I'm trying to figure out how this would work and so what I could see is our intention here is to essentially cover patients six months to two years of age who…where there's not an FDA approved indication or…but I think our intention is good, but I think we need to think about a prior authorization type structure for that particular comment because I think that what we will see is a mass exodus from people buying over-the-counter products, which would work perfectly well for them in most cases to now everybody wants their prescription product because they don't have to pay for it. And so I think that's the reality and I think we just…I don't think

that's our intention, however, so is there a way that we can structure this so that our intentions are to cover that special patient population and not completely open the door?

T. Vyn Reese: This is Dr. Reese. That was my question, too and they are dispensing loratadine. OTC is a drug to the Medicaid population that is being dispensed. So it's actually…it's coming in as a prescription…I assume you're writing prescriptions even though it's OTC they are delivering it as a drug and it is on the formulary now as our non-sedating antihistamine in that category and so that would cover it and that would make it a mute point. And that was my question, too. I think you've already answered that, Siri.

Jason Iltz: This is Jason, again, but remember there's more to consider than just Medicaid. There's uniform and all of those other structures where currently the formulary agent is loratadine OTC. Correct, Donna?

Donna Sullivan: Yes, that is correct.

Jason Iltz: So I mean it's not a mute point for the other organizations.

Donna Sullivan: Right now loratadine is OTC and it's not a covered drug because we don't cover OTC products. So if you made one of the others preferred with no stipulations then we would have an increase in use of the other… [end of Side B]

Donna Sullivan: …prescription product as well unless we had it on a form of prior authorization and usually what we do for a sub population on the Preferred Drug List is to put it on EPA for that population and then they can have it, you know, freely without any call or without any hassle.

Dan Lessler: And in this case we're really talking about the indication for the down to the six-months of age because loratadine covers the other two that were specified. So do we want to specify that the Washington Drug List should…actually, could we specify loratadine…well, actually how about the Washington Preferred Drug List should contain a product that is non-sedating and…you might not want to write this quite yet, Donna, category B and then say there should be, you know, there should be an agent that is FDA indicated down to six months that's provided with an expedited prior authorization or something like that. So just call out that one indication and say it needs to be available with expedited, prior authorization. Would that do it?

Siri Childs: Or just say for a special population and then that is how we would handle it. What you would say is…this is Siri Childs, for Washington Medicaid and what you would just specify is that for the special population of those children six months to two years a drug should be available that's FDA approved for that age group.

Duane Thurman: This is Duane. I would just caution not to be to the point where you're prescribing an EPA code, but if you just specify it as a sub population, special population then that would be what we would do according to our procedures.

Dan Lessler: Okay. Jason?

Jason Iltz: This is Jason. That's essentially what I was going to say is that we just need to specify the age range that it needs to be available for and then, you know, they can work on their end to put the appropriate things in place to manage it.

Dan Lessler: Okay. Are there other comments on this class? All right. So, actually, does somebody want to formerly put this forward as a motion?

Siri Childs: Dr. Lessler, could I just mention something else? Um, to follow…this is Siri Childs again. To follow up Duane's comment Washington Medicaid is going to be going to a newer computer system so it really would be beneficial to just point out the sub populations because in the future we would be able to put edits in our system that if the patient is, you know, six months to two years it will just be invisible and so it won't even have to have an EPA code or anything like that, you know, we'll be able just to take your recommendations and devise the edits to, you know, convey that clinical intent.

Dan Lessler: It appears…I mean…thanks for that information, Siri, it appears though that we're…as we've worded this we're okay in that regard. Is that correct? The Washington Preferred Drug List…

Siri Childs: Well, as long as you indicate that it is this specific population. That's what would be our cue on that.

Dan Lessler: Right. So is it adequate to say, "Must make available in an FDA approved product for patients six months to two years of age." Does that language…

Siri Childs: I'm hearing that we really would like to have the term special populations and then point that out.

Dan Lessler: Okay.

Siri Childs: For this special population of…

Dan Lessler: Right. Okay. All right.

Jason Iltz: This is Jason. So just to clarify now the way that this is worded from a management standpoint are we still okay to say that they can be subject to therapeutic interchange if one is listed as an EPA and the other is listed as loratadine OTC? Do you see what I'm saying? I mean do we get in trouble by saying that interchange? I mean I know non-preferreds are not interchanged, but if the preferred is OTC and then we have an EPA as well. How does that work?

Siri Childs: Well, what we usually do is DAW will override an EPA code as long as it's not a safety code. And so in this particular case I don't believe that…it's considered a preferred drug so I don't believe that it would be interchanged if you're talking about the special population one.

Duane Thurman: This is Duane Thurman. As a preferred drug it would not be…it wouldn't be effected by your decision to have them subject to therapeutic interchange. For the special population they would continue to get that drug.

Siri Childs: It's considered a preferred drug.

Jason Iltz: Okay.

Dan Lessler: Okay.

Siri Childs: But for that population.

Dan Lessler: All right. So, Carol?

Carol Cordy: Can you scroll down to the top? Well, scroll up. Just for consistency it looks like the wording needs to be changed in the beginning instead of just the updated information. Doesn't it have to say evidence of safety efficacy in special populations like they all do? I mean somehow we're changing this. We're just changing the format rather than having it the way it reads. And then I think there just needs to be a hyphen between non and sedating. And the drug list should contain…are we going to say a product that is or products that are? Non-sedating in pregnancy category B. It just says should contain product…

Dan Lessler: A product.

Carol Cordy: A product?

Dan Lessler: All right.

Man: It should be an before FDA instead of a.

Dan Lessler: So would somebody like to formerly put this forward as…you gotta put your insert…there you go. Would somebody like to formerly put this forward as a motion then for the record?

Jason Iltz: This is Jason Iltz. I'll go ahead and move this forward. After considering the updated evidence of safety, efficacy and special populations on newer antihistamines for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria, I move that cetirizine, desloratadine, loratadine and fexofenadine are safe and efficacious. The Washington Preferred Drug List should contain a product that is non-sedating in pregnancy category B and must make available an FDA approved product for the special population of patients six months to two years of age. Newer antihistamines can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria.

Dan Lessler: Thanks. Is there a second? Okay, it's seconded. A brief, friendly amendment. Is there…

Man: Shouldn't it read that…if you could go back…before pregnancy category B should not we be inserting FDA approved product again? It sort of reads there's a non-sedating and FDA approved product for pregnancy category B.

Dan Lessler: We'll take that as a friendly amendment.

Man: And then I'll second it.

Dan Lessler: And then you'll second it. Great. Okay. All those in favor say I.

Group: I.

Dan Lessler: Opposed same sign? All right. We're set and we're running right on time. So we're going to adjourn here until 11:00 when we'll come back to consider the triptans. Thanks.

Dan Lessler: Is Kim on?

Man: You could ask.

Dan Lessler: Kim, are you there? No. We're…why don't we wait just another minute. We're actually a minute or two early here. Kim, are you there?

Kim Peterson: Hello, this is Kim Peterson with the Oregon Evidence-based Practice Center.

Dan Lessler: Hi, Kim, it's Dan Lessler.

Kim Peterson: Hi.

Dan Lessler: Welcome.

Kim Peterson: Thank you.

Dan Lessler: So you're right on time. We have your PowerPoint presentation that's projected and right now we're looking at your title slide on…for the drug class of the triptans and if you want to go ahead and take it from there and just let us know when you want to change slides.

Kim Peterson: Okay. Great. So I'm going to be presenting the results of the current Oregon Evidence-based Practice Center drug class review on triptans, which is dated November 2005 and that's to be reflected on the cover slide. So hopefully we're looking at the same slides. So the presentation will reflect new evidence from the third update of this class and I'm going to be working off of a PowerPoint presentation that I'm hoping that I'm hoping you have the copy of, which consists of 30 slides.

Dan Lessler: Yes.

Kim Peterson: Okay, good. And because I know that your committee has reviewed this class before I was going to focus only on the slides that summarize the new evidence.

Dan Lessler: That's fine.

Kim Peterson: Okay. So I'll just let you know which slides I'm skipping to as we go along and let me know when you get there and so I'm going to start by skipping over slides two and three regarding our search strategy and the usual data collection and analysis methods, which haven't changed for update three. So I'm just going to go on to slide number four.

Dan Lessler: Okay.

Kim Peterson: Okay. So slide four details our inclusion criteria for populations and interventions. The thing to note here is that for update number three DERP elected to expand the intervention inclusion criteria to add subcutaneous injectables and nasal sprays. So we expanded the criteria for update three. So now I'll skip over slides five and six, which describe our inclusion criteria for outcomes, which didn't change for update number three. So let's just go to slide number seven.

Dan Lessler: Okay.

Kim Peterson: Okay. So I added this slide to just provide a recap of our previous conclusions and before we get started with the new evidence so we can be thinking about how the new evidence fits in and so as you may recall where we left off last time was with conclusions from previous meta-analysis and our re-analysis of numerous published and unpublished head-to-head and placebo-controlled trials all of which were indicating that both rizatriptan 10 mg and eletriptan 40 mg are superior to sumatriptan 100 mg and other similar triptans in reducing pain.

And at that point though we were still raising cautions about interpretation of the evidence from the head-to-head trials that were showing that eletriptan was superior to other encapsulated triptans in light of the continuing debate about the possible differential clinical effects of using unilateral encapsulations methods. Next slide, slide eight.

So the main types of evidence that we were hoping to find for update number three were head-to-head trials that compared eletriptan directly to other non-encapsulated triptans so conventional forms of oral triptans and we were also looking for head-to-head trials that compared any of the newly included forms of triptans, the injectables and the nasal formulations to other oral triptans. So that's the kind of evidence we were seeking to help inform us where we still had some questions. So let's skip to slide 11 that details the evidence that we found.

Dan Lessler: Okay.

Kim Peterson: Okay. So what we found were six new head-to-head trials and none of which compared eletriptan 40 mg to other non-encapsulated triptans. So the only new trial that involved eletriptan was with it dosed at 80 mg, which is not an approved dose in the U.S. So that evidence really isn't relevant to your decisions about eletriptan at this point. So we don't have anything new to add to our previous interpretations of the evidence for eletriptan. And then with regard to the other five head-to-head trials detailed in this slide they also didn't add evidence that changed our previous conclusions because all five trials suffered from either internal validity flaws and were rated poor quality so they're included and we did abstract the evidence from them into our evidence tables, but we didn't include the findings in our analyses.

And then the other four we didn't include in the analyses because they were comparing inequitable dosages of triptans. So a higher dose of one Triptan to a lower dose of another, or relatively lower.

Okay. So now that's really all of the information that we were able to glean from the six new head-to-head trials. So now I'm going to have us skip all the way to slide 21 where we're going to talk about the evidence from the new placebo-controlled trials that we identified and added for this update. So slide 21.

Dan Lessler: All right. We're there.

Kim Peterson: Okay. Because the rest of the slides in between just go over the details of the previously discussed and included head-to-head trials. That's why I skipped over those. You've seen that evidence before. So…well, actually what this slide is going to look at is new evidence that we…new placebo-controlled evidence that we looked at to try to address some gaps in the head-to-head trial evidence. So while you know there are numerous head-to-head trials available in this drug class, which is great, analyses of real-life functional capacity, work productivity and quality of life types of outcomes were lacking in this trials though. And so to date we've only been able to find these kinds of outcomes reported in the placebo-controlled trials and observational studies and although there's a lot of evidence, there is such diversity and outcome reporting methods that it hasn't been sensible to try to perform any indirect analyses based on these trials and observational studies. So we don't have any information about comparative efficacy of triptans on these real-life effectiveness outcomes. So for update three I'll just note that we identified and added additional placebo-controlled trials of subcutaneous sumatriptan, but this evidence still didn't provide any new information about comparative efficacy. So what you can learn from these trials is that, yes, subcutaneous sumatriptan does indeed improve these types of outcomes as does eletriptan and rizatriptan in other placebo-controlled studies. So that's a good thing to know that those outcomes have been studied for those triptans, but we just don't know anything about how they compare to one another on these outcomes. Okay? So now let's skip to slide 26.

Dan Lessler: Okay.

Kim Peterson: Okay. So that was short, but sweet and that's really all the new evidence we found related to effectiveness and efficacy. So I'm going to move along to looking at the new evidence for safety outcomes and so to recap. Previously our findings were that there were no consistent differences in head-to-head trials between different triptans in adverse affects such as chest pain and tightness, dizziness, paresthesias and somnolence.

And for update three the evidence from the six new head-to-head trials didn't impact that previous conclusion. Again, for the same reasons discussed earlier that they were either poor quality or compared inequitable dosage levels of different triptans. So now let's skip to slide 28.

Dan Lessler: Okay.

Kim Peterson: Okay. And again pretty straight forward here. Previously we had no direct evidence of comparatively efficacy, effectiveness or safety of triptans in subgroups of patients of differing age, gender or race. And we didn't find any evidence in update number three either. So we really…there's just inadequate information to try to draw any conclusions for key question three. So next slide, which actually be the last slide for this presentation. Um, just reiterating the information I just presented and that is that we made no changes to our previous conclusions based on the new evidence we identified in the third update of this class. And so we still have two main questions that are unanswered and those again are: (1) how does eletriptan compare to clinically to other non-encapsulated triptans? and (2) and how do nasal, injectable and oral disintegrating tablet triptans compare to other triptans? So in any future updates of this class, which none are scheduled at this point, we'll still be looking for that evidence to fill those gaps. So that concludes my presentation of this evidence. What are you questions?

Dan Lessler: Thanks. So um, Kim, yeah, I was going to open it up here to P&T committee members to see if they had any questions for you in terms of points of clarification. It does not look like we have any…and if you can stay on the line just for a moment. We were now going to take stakeholder input and I'm just getting a list of stakeholders that wanted to comment. So hold on here.

Kim Peterson: Okay.

Dan Lessler: So Kim if you could just stay with us for a bit more it's sometimes helpful to have you hear the stakeholder comments. Sometimes questions arise that we like to go for you for clarification on.

Kim Peterson: Sure.

Dan Lessler: Thanks. So just to remind people, again, that if people could identify who they are representing, what organization they are from and if you're not from any particular organization if you are getting sponsorship if you could please let us know. And then I ask that you please limit your comments to three minutes. So the first person signed up is Dr. Brzana(?).

Jennifer Brzana: Good morning. My name is Jennifer Brzana. I'm a PharmD and a regional medical scientist with GlaxoSmithKline. I thank you for the opportunity to discuss the continuing position of sumatriptan's status on the Washington State Medicaid PDL. Sumatriptan is the most widely studied triptan on the market and therefore possesses a vast library of safety and efficacy data and this data allows me to bring to your attention three pertinent points to think about when considering sumatriptan's status on the PDL.

Point one is unsurpassed pain-free efficacy. The [inaudible] triptan report discusses some of the shortcomings with available triptan data specifically that's over reliance on pain relief or reduction in pain to mild pain as an outcome measure in migraine trials. It sights a study done by Lipton, et al, which simply asked migraine patients what they wanted most from their migraine therapy and the number one response was patients wanted to be pain free.

In 2004 the Carpe(?) study was published in clinical therapeutics, which found that 75% of patients who treated early with reformulated sumatriptan were pain free at two hours. It's also important to note that no head-to-head trial data to date has been studied using any triptan compared to this reformulated sumatriptan. So all head-to-head comparative data has utilized the old tablet, the conventional tablet formulation, which is no longer commercially available.

Point two, sumatriptan is now the most rapidly acting oral triptan on the market. Again, if we look at the Lipton study the third most important thing to migraine patients was rapid onset of pain relief. Well, sumatriptan reformulated tablets now have an onset of 20 minutes, which makes them the first oral triptan to surpass the 30-minute onset point. As always, onset of pain relief begins as early as 10 minutes with the injectable and 15 minutes with the nasal spray.

Point three, sumatriptan is the only triptan available in three different formulations. This allows patients to tailor their treatment to the specific migraine symptoms they are experiencing. This utilization of the strategy is unique to sumatriptan since we know that code administering to different triptans in the same 24-hour period is contraindicated. It's again important to note since earlier this year sumatriptan stat dose injectable has also been available in a 4 mg dose in addition to the always available 6 mg dose. Again, just expanding opportunity for patients to tailor treatment to their specific needs.

To conclude, as these three points illustrate, sumatriptan offers unsurpassed pain free rates at a rapid onset. The multiple formulations of sumatriptan allow patients to utilize a stratified care approach and these three points allow sumatriptan to remain the gold standard for treatment migraine headaches. Thank you.

Dan Lessler: Thank you. Are there any questions? Thank you. Next is Dr. Robinson.

Dr. Robinson: Hello. I practice neurology and specifically focus my clinical practice on headaches for the past three years. And as we all know migraines are very heterogeneous disorder, every single individual essentially has very

specific headache to themselves. I was at this meeting a year ago and supported Relpax formulary and today the purpose of my being here to continue to support Relpax formulary. When we consider medications for any particular patient and any particular clinical scenario their purpose of the treatment is to provide obviously improved symptoms, improved functionability, the patient would be able to return to work or, you know, basically activity of normal living and although majority of the triptans have been shown to be very efficacious there are big differences of how patients tolerate the treatments and what type of specific migraines that it can be used for. Relpax can be successfully used for nocturnal migraines, perimenstrual migraines and episodic migraines and that covers quite a lot of territory. Because it is an oral medication patient's fear of using subcutaneous injections also is addressed as well. It is really a very efficacious drug and has an excellent side effect profile. And for me the practicing headache specialist and neurologist it has proven its efficacy so to speak in clinical practice and in the trenches. For most of my patient's prescription for a month lasts for a month as opposed of one week or two weeks as the case with Maxalt or Imitrex can be, which is why I think that it should be…continue to be available for my patients. Thank you.

Dan Lessler: Thank you. Again, any questions? No. Okay, thank you. Next is Dr. Conley.

Dr. Conley: Good morning. I'm Dr. Conley with Ortho McNeil Janssen Scientific Affairs. I'm here today to discuss the use of Axert in the acute treatment of migraine and I have three brief points. First is that Axert has been shown in many clinical trials to be safe and tolerable. The most common side effects with Axert reported in clinical trials are nausea, paresthesia and dry mouth. These occurred at a frequency similar to placebo. As the last speaker mentioned tolerability is extremely important to the patients in the continued use compliance and effective treatment of migraine. There is a low incidence of both central nervous system side effects and chest symptoms also reported with Axert.

Secondly, Axert has been shown to be effective in the meta-analysis of over 24,000 adult patients from randomized double blind placebo-controlled or active-controlled trials. The authors of that meta-analysis conclude that Axert 12.5 mg, Relpax 80 mg and Maxalt 10 mg provided the highest likelihood of consistent efficacy. Of those three Relpax 80 mg is not an approved dose in the U.S. The authors state that Axert 12.5 mg is the choice for both high tolerability and for efficacy.

And thirdly I just want to highlight to the committee the importance of having more than one triptan available on the Preferred Drug List. The published literature suggests that not all patients respond to the initial triptan, but do subsequently respond to a second triptan agent. So with regard to Axert underscoring this point, a randomized double blind study was conducted to evaluate the response of an acute migraine attack to Axert treatment in patients who had at least two failed responses to Imitrex. During their first acute migraine attack 300 patients received Imitrex 50 mg. Of these 73% did not respond to the Imitrex. Those patients who did not respond were then randomized to receive Axert 12.5 mg or placebo for their second attack. Almost half of the patients taking Axert and 23% of those taking placebo did receive pain relief on that second attack, which was a statistically significant effective Axert versus placebo.

With regard to treatment emergence adverse events and that also again Axert was similar to placebo in the treatment emergent adverse events. So this study just underscores the safety tolerability and efficacy of Axert and the importance of having more than one agent on the Preferred Drug List. Thank you.

Dan Lessler: Thank you. Are there any questions? All right. Thank you. And finally Dr. Conner.

Dr. Conner: Good morning. Dr. Conner with the Clinical Education Division with Pfizer. Before I start I would like to commend the committee for their work today and their continuing work on these drug reviews. I'm here to talk today about eletriptan or Relpax, which is the only triptan to show superior efficacy versus sumatriptan 100 mg in multiple, well designed, controlled, head-to-head clinical trials. Now while the Oregon EPC report does in fact acknowledge these data and that's found on pages 17, 18 and 19 of the updated report number three, the authors discount the results of these studies in part because they perceive an issue with the

tablet blinding, which is the method used that required sumatriptan 100 mg be placed within in a gelatin capsule to both maintain double blinding and also to eliminate any observational bias.

The evidence-based practice report concludes an encapsulation of sumatriptan may have reduced its efficacy therefore potentially biasing the results in favor of eletriptan. While there are four separate lines of evidence that support placing sumatriptan within a gelatin capsule does not substantially effect the clinical efficacy of the product. We've got in vitro dissolution testing, we've got in vivo dissolution testing, we've got bio equivalent studies using the same standards set by the FDA for bio equivalence and we have consistent clinical data if you look at the therapeutic gain or placebo subtracted efficacy. It's right in line with the totality of published data.

The authors of the evidence-based practice report though did conclude or conduct their own meta-analysis to actually address this issue and that meta-analysis can be found on pages 14 and 15 of your report. In this analysis the EPC office concluded that and I quote, "For all triptans encapsulation was consistently associated with decreased efficacy except paradoxically the efficacy of eletriptan was increased." However, when you look closely at this meta-analysis and the table, which is table 5, again on your report on page 15 you'll find that though the average efficacy rates are different than 95% confidence intervals. The 95% confidence intervals for both eletriptan 40 mg encapsulated and unencapsulated and sumatriptan 100 mg encapsulated and unencapsulated do overlap. What this indicates is that while there's a numerical difference, this difference is not statistically significant. And I encourage the authors of this report to further clarify and elaborate upon their meta-analysis. However, in light of any vetted, pure of viewed, manuscript describing the very analysis that's in this report we can only conclude that encapsulation did not result in any significant reductions or increases for that matter in the efficacy of eletriptan or sumatriptan. That said I urge the committee to re-evaluate the head-to-head data showing that eletriptan is the only triptan to demonstrate superiority versus sumatriptan 100 mg in multiple, well designed, controlled head-to-head trials. And again those data are in this report on page 17, 18 and 19.

I'd like to finish by highlighting two points sited in the evidence-based practice report.

Dan Lessler: I would ask you to end it here. You're out of time.

Dr. Conner: Okay. Well, in light of those evidence I just urge you again to reconsider or to consider maintaining access to Relpax.

Dan Lessler: Thank you. Are there questions from the committee? Kim, are you there?

Kim Peterson: Yes.

Dan Lessler: So, um, I was going to ask if you would just be willing to comment. I know this has been an issue in terms of these different preparations since the initial report. But I was wondering if you wanted to just comment on the comments that were just made about encapsulation?

Kim Peterson: Sure. I would say that we've heard these comments before and we don't disagree with the studies that the speaker was referring to regarding the pharmacokinetics and the therapeutic difference. We, in fact, I think refer to those in our report. Our focus is always on clinical outcomes and has always been that the gold standard would be to compare one drug…a study…a trial that compared one drug directly to another. So we would…we've always wanted to see a head-to-head study that compared eletriptan directly to unencapsulated sumatriptan 100. You know, that would really answer the question definitively.

As for our meta-analysis the speaker did refer to the results and one of the issues has been that this has not been published in a [inaudible] view journal and we are working on that and hope to have that published in a [inaudible] view journal to address those concerns and we've also…we're also adding new evidence from update three to that meta-analysis and so we appreciate that criticism and we agree with that and we're continuing to be in the process of putting together that publication.

It has always been that…we present our findings of our meta-analysis in our review but then it's always up to the individual P&T committees as to how much they…how much importance they want to place on those findings. So that would be my final message is that, you know, there are questions about…as the speaker raised overlapping confidence intervals that would suggest that while we can't rule out that there…there's part of the confidence interval that doesn't overlap we can't rule out that there is a difference there. But we also…so it's likely that there…it's equally likely that there is a difference or that there isn't a difference. So that's really up to the committees to make an interpretation about that. Right now our position has been that it's just raising a question for us. So we're not ruling out that there could be…that eletriptan could be superior and for now we're just acknowledging that it's clearer that it's as effective sumatriptan. We're just still trying to answer the question of whether we can defend…we can conclude that it's in fact superior. So those would be my comments.

Dan Lessler: Okay. Thank you. I was going to ask if there are any other questions from the P&T Committee for Kim? No. So, Kim, thank you very much for your presentation and staying with us for the discussion here. We can let you go now.

Kim Peterson: Okay. Great.

Dan Lessler: Take care.

Kim Peterson: Bye.

Dan Lessler: So once again I think people have the previous motion that's in their books from March of 2005. Maybe we can start there and take a look and I guess by means of getting the discussion started again would ask if there are any comments on that existing motion and based on what we've heard any thoughts about modifying it in any way?

Carol Cordy: Carol Cordy here. I just have kind of a side bar question. With this class of drugs it seems like the dosages are so varied and when we talked about the therapeutic interchange before I think the Pharmacy Association of the State was going to develop some kind of guideline. I'm just wondering what the status is of that on triptans and how do they deviate exchanges?

Siri Childs: This is Siri Childs. I haven't checked currently but there were clinical pearls(?) developed for these first drug classes to help the pharmacists with the therapeutic interchange. Has any of the other pharmacists seen those recently? They are available as I know to the pharmacists now.

Dan Lessler: Janet?

Janet Kelly: Yeah, I haven't looked at them in the last, you know, six months, but they were up on the web site and available. I don't think that this is a class that people have had, pharmacists have had a particular trouble, you know, it's not…I mean yes the doses are different, but they are not particularly problematic. I mean as far as some of our other classes are a lot more difficult than this.

Dan Lessler: Okay. Thanks. Other comments or thoughts, Bob?

Bob Bray: This is Bob Bray. The comment I was going to make is, you know, in the current all different means of delivering the drug is present—oral, dissolving, tablet and inter nasal and subcutaneous. I think that would be valuable to continue as I wonder if we want to state that in our motion?

Dan Lessler: That the different methods of administration…

Bob Bray: That each of the delivery…yeah, yeah.

Dan Lessler: Are there other thoughts about that in terms of modifying the existing? Seems like…okay. So that might be one change.

T. T. Vyn Reese: Hi, it's T. Vyn Reese. The question is, "Is it different to have an orally dissolving tablet versus a…one that you actually swallow." And is it different to have…it is different to have inter nasal and subcutaneous. So those are two…so actually there would be like four different delivery systems. One would be oral dissolving, one would be PO conventional, one would be inter nasal and one would be subcutaneous. So there would be four different ways to administer these products. Is that what you're saying, Bob, that you want all four of those?

Bob Bray: Yes. I think patients who vomit early in their migraine would…maybe prefer the dissolving tablet over an injectable or a nasal and then there's…and other people would prefer one or the other for purposes of being able to tolerate the drug.

Dan Lessler: Other comments in terms of thoughts about modifying the existing motion? So it sounds like, Bob, what you're saying is essentially keep the existing motion, but specify the availability of each of these different modes of administration?

Bob Bray: Okay.

Dan Lessler: Okay. So would you like to… [end of Side A]

[Side B]

Bob Bray: So I'll just read the first part. After considering the evidence of safety, efficacy and special populations for the treatment of migraine, I move that almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan are safe and efficacious. The Washington Preferred Drug List must contain…it's great that you can read my mind.

[laughter]

Bob Bray: Must contain an oral, oral dissolving, nasal and subcutaneous product. No single triptan is associated with fewer adverse events in special populations. The above-named triptans can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of migraine.

Dan Lessler: Okay. Is there a second? A second by Ken. Okay. Any other comment or discussion at this point? Okay. Why don't we go ahead and vote. All those in favor say, I.

Group: I.

Dan Lessler: Opposed. Same sign. Okay. So the motion passes and we actually finish a bit early. I'm assuming at this point, Jeff, that we should probably skip to…take a longer break or what?

Jeff Graham: That's correct because Roger Childs scheduled for 1:00.

Dan Lessler: Okay. So we will adjourn until 1:00. Thanks.

Roger Childs: …and interventions and outcomes assessed and it just wasn't possible to do that for this set of studies. Um, next slide. so getting into the results, um, so the main results for efficacy…there were five head-to-head trials of long-acting opioids. Two of those were new for this update. So one of them was this first trial that's listed. It's a trial of transdermal fentanyl versus oral morphine. It's actually the biggest trial – 680 patients. It's also the longest available trial. So 13 months. It was rated fair quality and it included patients with chronic low back pain who weren't on regular strong opioid. It found that the two drugs were similar for efficacy. There was a trend towards more withdrawals on fentanyl, but that was not significant.

There was also a poor quality trial of the same comparison. It actually had the same lead author. This was included in earlier versions of this report. That one was rated poor quality because many of the patients had previously been on oral morphine and it wasn't a blinded study. We thought that really made interpretation of the results very difficult and that was in various pain conditions. It found that pain control was better with fentanyl but there was also a trend towards more withdrawals. So somewhat mixed findings. There was also a very small fair quality trial with patients with chronic pancreatitis. I think they had like 20 patients who found no differences.

The other new trial or new head-to-head trial at least was oxymorphone versus oxycodone that found no differences in efficacy.

Another trial we included in previous reports that was once versus twice daily oral morphine. No differences for pain control using the once daily morphine in the morning was superior for one out of seven sleep measures. There were no other differences on any other outcomes.

Next slide. So trials of long-acting opioids versus placebo or non-opioids we found 20 trials. Only two were rated good quality. Both of those were in patients with neuropathic pain. One was a six-week study of a long-acting oxycodone that found that drug superior to placebo. There was also a multi…a multiple cross over trial of morphine gabapentin – both were placebo so patients would get each of those. That found morphine superior to placebo as well. Among the 20 trials there was diversity in the populations, interventions, and the assessed outcomes. Really unable to draw conclusions about comparative efficacy from indirect comparisons using these types of studies. They are just too different in terms of what they are looking at and how they evaluated patients.

There were two trials I just wanted to mention because these are the only trials available of these two drugs. One is of high versus low dosed levorphenol. One other one was of methadone versus placebo. Both for neuropathic pain and both showed efficacy but they both kind of used unusual methods. In particular the

methadone trial; this was a study that gave patients randomly methadone every other day with no drug on the in between days. So one day you would either get methadone or placebo, the next day you'd get nothing and you would do that several times. I can't remember how long the trial was—two weeks or something like that. And they were assessing outcomes on the, you know, days after they had gotten methadone or placebo. So very, you know, not how we give methadone in clinical practice, but it's the only trial of methadone that's available. The levorphenol trial didn't have any placebo arm. They kind of used this low dosed levorphenol as the placebo arm and compared it to high dose. Again, making it very difficult to compare results with other active controlled or placebo controlled trials.

Next slide. We found seven of the trials noted in the previous slide looked at long-acting versus short-acting opioids. So they were a subset of the 20 trials. None of the trials were rated good quality. Again, this looked at heterogeneous populations, interventions and assessed outcomes. There were no consistent trends favoring either long or short-acting opioids. A subset of three trials comparing long and short acting oxycodone was more homogeneous and also found no differences.

Next slide. In terms of safety first with the head-to-head trials one of the trials, the very small trial of chronic pancreatitis patients didn't report any safety data. So that wasn't included so that left four head-to-head trials. None were rated as good quality for safety evaluation. The newest trial of the transdermal fentanyl versus oral morphine, again, this is the largest and longest study available found that constipation favored fentanyl but overall withdrawal due to adverse events there was a trend towards morphine being favored. And it's not clear from how the studies reported what explains the increased, you know, morphine had more constipation but it had a trend towards decreased withdrawal due to adverse events and it's not clear what accounts for that difference. But this is, you know, this is sometimes a problem with studies that focus on one or two adverse events and don't give enough detail about others. We just can't tell, but withdrawal due to adverse events we usually consider as being a market for serious or intolerable adverse events. So I think the difference here in terms of fentanyl being favored for constipation but not being favored for overall withdrawal due to adverse events, you know, makes it difficult to interpret those results.

There was another trial…the other new trial of oxymorphone versus oxycodone was rated poor quality for adverse event assessment, but found no differences and then the once daily versus twice daily morphine constipation favored twice daily. Asthenia favored once daily withdrawal due to adverse events were equal. So again kind of mixed findings.

Next slide. For studies of long-acting opioids versus placebo or non-opioids 19 trials reported adverse event data. None of the trials were reported…excuse me, none of the trials were rated good quality. There were very broad ranges for adverse events for each long-acting opioids and there was overlap between the drugs. Probably, you know, more indicating differences in kind of quality of adverse event assessment rather than true differences between the drugs. There would be some trials that would report, you know, zero to 10% rates of nausea or vomiting and others would report, you know, 60% or 70% for the same drugs at the same doses, which just makes you think that they're, you know, really doing different things when they're defining or assessing for these adverse events. There was no pattern that suggested increased safety for any particular long-acting opioids from these studies, but really inadequate data to make many judgments from the available evidence.

Next slide. So studies of long-acting opioids versus placebo or non-opioids. We also looked at observational studies. We included 13 observational studies – two were fair quality retrospective cohort studies by the same investigators that looked at California Medicaid patients and found that constipation with long-acting oxycodone was more frequent than with transdermal fentanyl, but there was no significant difference compared to long-acting morphine. Now this is a trial…excuse me, these were studies that we found difficult to interpret because there were really large baseline differences between the groups receiving different drugs. And like we mentioned before for the head-to-head trial they had a very narrow focus on a single adverse event. So, you know, you don't know for example if other adverse events are increased or decreased for the different drugs. In terms of the populations, I mean the patients that were receiving transdermal fentanyl were significantly older. They tended to be on other drugs, you know, demographics in terms of racial

proportions and things like that were really different. And they adjusted for this in the study, but, you know, we worry about unmeasured confounders effecting results even when we know what they are and can adjust for them well when they are obvious that there are such differences to start with. It really makes you worry that there is other stuff that we're not able to adjust for or even know about.

There are 11 other observational studies. They were generally of worse quality than the trials. A lot of them were kind of extensions of the trials that just followed patients out for longer periods of time and they didn't really give any more useful data on comparative safety.

Next slide. There's a couple of other observational studies we want to mention. One is the ongoing Drug Abuse Warning Network study where we found…which found increased E.R. mentioned through 2001 for opioids. So this is patients presenting to an emergency room with, you know, an overdose or some other problem, which is not related to opioids. So fentanyl mentions increased by 641%, but the absolute rates were still very low with fentanyl. Morphine by 113% and oxycodone by 347%. An earlier study looked at the rates of prescriptions of these different drugs and it also found that the prescription rate had increased. So it actually isn't clear if the increase in the proportion is simply due to increased, you know, prescription rates rather than that one of the drugs is actually more dangerous than others. There are several other issues with the Drug Abuse Warning Network study. One is that the study does not distinguish between long and short acting drugs. So you can't tell, you know, what formulation patients were getting. It's also not clear from most of the reports what conditions people were being prescribed drugs for or if they were street using drugs. So it's difficult to get that kind of information from it. But it is a national study and it, you know, we think it's important to continue following this because it may give some information about trends nationally about abuse and overdose and those kinds of things. The other thing to know about the DAWN study is that they've kind of revamped their methodology and, you know, the last we looked, which was in the spring of something like that…they hadn't published the results with the new methodology, but new results may not be directly comparable to older results from DAWN.

Next slide. The State of Oregon also found that methadone associated deaths increased from 23 in 1999 to 103 in 2002. Prescriptions also increased five-fold over that period. Similar data has been reported from other states as well. And again the idea of being that…the increased deaths that are being seen seem to be associated with increased prescription rates not to, you know, the medication being used more dangerously or something like that. There was a case series of 96 methadone associated deaths reported from 1992 to 2002 in Hennepin County, Minnesota. 15% were in chronic pain patients. The study reported no data on prescribing patterns though.

Next slide. The last part on safety was looking at long-acting versus short-acting opioids. Again, this is a subset of seven trials and none of the trials were rated good quality for adverse event assessment and there was no clear pattern favoring either long or short acting opioids.

Next slide. Subpopulations – so we tried to look at all those subpopulations to see if comparative effectiveness varied according to age, race, gender, type of pain. Patients at high risk were generally excluded from these studies. So really couldn't evaluate that subpopulation. And there was really almost no information on subpopulations. In the study that looked at specific types of pain, some looked at neuropathic pain for example and others looked at non-neuropathic pain. You basically end up with the same, you know, types of results as we had before meaning generally inadequate evidence to prove, you know, differences in efficacy or safety and you just have fewer studies. So even harder to make, you know, clear judgments. So we couldn't come to any definitive conclusions about different effects in different sub populations.

Next slide. Just want to mention several excluded trials of interest. There were three short-term placebo-controlled trials of transdermal buprenorphine, but that's not available in the U.S. yet. Most of the available data is in cancer pain patients so far. I actually don't know…I couldn't find on the FDA web site if this drug was going through the FDA approval process, but we haven't seen anything yet. The other drug, long-acting hydromorphone as I mentioned at the beginning, it's currently not available because of problems/ concerns

about rapid absorption if you mix it with even small amounts of alcohol, but the available studies are only abstracts and/or cancer patients so they don't meet inclusion criteria anyway.

Next slide. So just to summarize the update on long-acting opioids for non-cancer pain. There's only five head-to-head trials. One is rated fair quality. They found that the drugs that were compared were similar for efficacy and there were some mixed results for safety adverse events. In particular a transdermal fentanyl in some studies appears to be associated with a lower risk of constipation although not for a lower risk of overall adverse events or withdrawal due to adverse events. We await trials of long-acting hydromorphone although currently it's not available in the U.S. There's only one trial of levorphenol and one placebo-controlled trial of methadone. Both in patients with neuropathic pain and again as mentioned before those results aren't comparable to other studies because of issues with design. There's generally poor adverse event assessment quality in these qualities and there's no evidence that one long-acting opioid is superior to others or that long-acting opioids as a class are superior to short-acting. There's also no data on comparative risk of addiction or abuse.

I think that's it. So if there are any questions.

Carol Cordy: Thank you, Roger, that was excellent. Is there…are there any questions from the committee? Roger, can you stay a few minutes if there's some discussion after the stakeholders?

Roger Childs: Yeah, I'm happy to.

Carol Cordy: Okay. We have two stakeholders. Is there anyone besides Dr. Dermot Fitzgibbon and Carrie Aaron that didn't get your name on here? Okay. Dr. Fitzgibbon? And if you could say who you're representing and if you're representing any pharmaceutical company.

Dermot Fitzgibbon: I'm not representing a pharmaceutical company. My name is Dermot Fitzgibbon. I'm a physician at the University of Washington's Seattle Cancer Care Alliance. I really have no invested interest in any particular opioid, but I have a vested interest in using opioids for cancer patients and my biggest concern is that if we restrict opioid use to two types—extended release morphine and methadone, this is going to be a real problem for the long-term management of many of the patients that I see.

Many of the patients that I see are cancer patients, but the cancer patients that I see typically have chronic problems and when we prescribe opioids for these patients we expect these patients to be on opioids for a long time. The data that I have seen regarding methadone use, I think is particularly problematic. I have seen situations where conversions from various long-acting opioids to methadone are inappropriate and the doses are too high. I would strongly recommend to the committee that we keep open the large variety of long-acting opioids that are currently on the market and I would ask you not to restrict medication use to the two kinds(?) proposed.

Carol Cordy: Thank you.

Jeff Graham: This is Jeff Graham. I just wanted to comment to you that all cancer patients are excluded from this study and that cancer patients can receive any of the long-acting opioids.

Dermot Fitzgibbon: If I may answer that. We have not been seeing that in our practice. We have found increasingly that there are restrictions placed on oncology patients who have a diagnosis of chronic pain and the tendencies that we've been seeing recently is that if you do not have a diagnosis of tumor-associated pain there are increasing restrictions from a variety of different sources in our prescription practices.

Jeff Graham: Thank you. We'll pass that information on to our Medicaid agency.

Carol Cordy: Carrie Aaron?

Carrie Aaron: Hello. My name is Carrie Aaron. I'm a licensed veterinarian. I'm also the Associate Director for Clinical Development and Education in the Scientific Affairs Department at Endo Pharmaceuticals. The purpose of my prepared comments today is to provide an update and to ensure the committee's awareness of events which have transpired since the issuance this past April of the Oregon Evidence-based Practice Center's final report of it's long-acting opioid analgesics drug class review.

On June 22nd of this year just shy of two months ago the FDA granted final approvals for two new opioid oral formulations and these were the unique opioid oxymorphone hydrochloride. These formulations consist of an immediate release oral formulation of oxymorphone now known under the trade name Opana tablets and in extended release oral formulation of oxymorphone now known under the trade name Opana ER tablets.

It is important to note that oxymorphone as a molecule is chemically and pharmacologically distinct from all other opioids including those currently listed on the Washington State Preferred Drug List. Specific to the extended release version of oxymorphone it is believed that the Opana ER clinical program represents the most comprehensive clinical program of any long-acting opioid analgesic upon FDA approval. The program consists of 15 phase two and phase three clinical trials representing more than 2,000 patients across a range of chronically painful conditions including cancer pain, osteoarthritis pain and low back pain. Additionally, studies were conducted in the vastly clinically dissimilar opioid naïve and opioid experienced populations.

Lastly, the Opana ER clinical program is the first to demonstrate durability of analgesic effect through the inclusion of three-month pivotal clinical trials in both opioid naïve and opioid experienced patients suffering from chronic low back pain. While it is understood that the committee has not at this time had the opportunity to benefit from a full review of the Opana ER data, we felt it important to bring this new long-acting opioid option to your attention in hopes that in looking towards the future the unique clinical need for choice within the long-acting opioid class will be given serious consideration. As you know, there are a number of important chemical and genetic variables determining how each individual patient responds to an opioid with respect to both analgesic efficacy, as well as tolerability. The availability of additional choice in the long-acting opioid medication class would enable optimization of each individual's pain management regime and increase the likelihood of successful clinical outcomes. Thank you very much.

Carol Cordy: Thank you. Roger, did you have any comments on the last speaker's…

Roger Childs: Yeah, I can say for oxymorphone that we did a separate search for oxymorphone and hydromorphone so in addition to kind of our previous searches, you know, that focused on the drugs that were available at the time we actually did a specific search on hydromorphone and oxymorphone and as I mentioned in the summary we included that head-to-head trial of oxymorphone versus oxycodone. We found no other published, you know, studies at that time. There may be others now, but we didn't find any when we…and obviously FDA hadn't approved it so they didn't have anything on their web site yet. So there may be newer stuff out there, but we haven't seen it yet.

Carol Cordy: Okay. Thank you. Are there any questions from the committee? So I guess we'll go, Roger, thank you very much.

Roger Childs: Thank you.

Carol Cordy: So I guess if there's no discussion…do we have the previous motion or motions here?

Donna Sullivan: This is Donna Sullivan. This is the motion that you made in 2004. The motion in 2005 basically states that you're renewing this motion. So I'm showing you the one from 2004, which is more explicit.

Carol Cordy: And it looks like on the next page there's a template if we want to change this to match the templates of the others. Somebody want to take that on?

Jason Iltz: This is Jason. Just for a point of clarification are we still to consider this as a review for specifically non-cancer pain? If yes, we will need to add this in. No, thank you, we've already done that. Maybe I should look up. Mine doesn't say that.

T. Vyn Reese: This is Dr. Reese. It doesn't look like we have a lot of new evidence to work with and so I don't see that we should make a different conclusion or come to a different conclusion than we did when we last considered this a year ago. So I would move that we just basically make the same motion that we did in 2004 and 2005 for…so I'll just read it as written. After considering the updated evidence of safety, efficacy in special populations for the treatment of non-cancer pain, I move that transdermal fentanyl, oral oxycodone, morphine, methadone, levorphenol, codeine, dihydrocodeine, hydromorphone and oxymorphone are safe and effective when a single long-acting opioid is associated with fewer adverse events in special populations. Long acting opioids can be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of non-cancer pain. Again, this is non-cancer pain only. Cancer patients should be a separate category and there shouldn't be therapeutic substitutions or interchanges for those patients. That's a little bit of editorializing on the side, but anyway this is the motion before us. Thank you.

Carol Cordy: And this is just a comment. Carol Cordy. This is different from the motion on June 16th because it's in the new format. So I think…and the previous ones did not talk about therapeutic interchange.

Janet Kelly: These are scheduled too. There's no therapeutic interchange by a pharmacist.

Man: Right. Carol, I was going to state that we don't have therapeutic interchange.

T. Vyn Reese: Right. They shouldn't be interchanged. I was just reading along with it.

Carol Cordy: So we need to delete…

Janet Kelly: Cannot be…

Jason Iltz: Instead of deleting just say cannot.

Carol Cordy: Or just leave it out.

Jason Iltz: Again, this is Jason. I'll make Carol's edit for her before she does it rather than effective let's say efficacious and then after that I think I would prefer efficacy—sorry, no efficacious. And then on our previous motions

we had a statement that said when used appropriately and have similar adverse effects, which I think may be appropriate for this particular class.

Bob Bray: This is Bob Bray. The previous motions talked about making sure that we had more than one drug in this class. That's been the case, but I think we should re-state that. I think that it would be inappropriate to have only one and in particular I think it would be very inappropriate to have only methadone.

T. Vyn Reese: We should add…there should be more than one preferred drug in the long-acting opioid class. That's…I basically wanted to re-do just the 2004 motion. So…and that's part of the motion is there should be more than one preferred drug in the long-acting opioid class.

Carol Cordy: Do you think we need to say similar adverse effects in the third to the last… Are there any other edits or suggestions?

Woman: In the second to the last sentence it should be long-acting instead of long action.

T. Vyn Reese: Any other additions? So we'll rephrase the…or re-read the motion. After considering the updated evidence of safety, efficacy in special populations for the treatment of non-cancer pain, I move that transdermal fentanyl, oral oxycodone, morphine, methadone, levorphenol, codeine, dihydrocodeine, hydromorphone and oxymorphone are safe and efficacious when used appropriately and have similar adverse events. There should be more than one preferred drug in the long-acting opioid class. No long-acting opioid is associated with fewer adverse events in special populations. And that's the motion before us.

Jason Iltz: This is Jason and I'll second.

Carol Cordy: All in favor?

Group: I.

Carol Cordy: Opposed? The motion passes.

Jeff Graham: Carol, this is Jeff Graham. I'm trying to get the next presenter here early, but I haven't been able to do that yet.

Carol Cordy: Okay. So we'll break until 2:15.

Jeff Graham: Most likely, yes.

Carol Cordy: Okay. We'll break until 2:15.

George Allen: …next slide – safety outcomes looked at overall adverse events or ADR reports. So extent of patients in a particular trial who had an adverse event. Although the number or percent of patients who withdrew from the study due to an ADR. We also looked for reports of serious ADR and there were a few adverse reactions that we were specifically looking at because they were particularly associated with macrolides. So the first of those would be gastrointestinal adverse reactions, the nausea, vomiting, diarrhea, etc. And then a much

rarer, but included because of its seriousness ADR was prolongation of the QT interval, which is associated with torsades de pointes, which is a particular type of ventricular arrhythmias. So we included that because of the serious and notable effect of the macrolides.

Next slide. Subgroups – we did do subgroup analysis to look at whether the macrolides [inaudible] and efficacy if you broke it down by subgroup analysis – so the subgroups that we looked at were demographics: age, gender, ethnicity; presence of concomitant medications; also presence of co-morbidities; and then finally pregnancy.

Next slide. If you want to interrupt with any questions at any point, you know, feel free of course. Studies design, inclusion criteria as far as study design for effectiveness or efficacy outcomes. We looked at controlled clinical trials to randomize clinical trials and we also looked at systematic reviews and reference lists of those systematic reviews if they were good quality or adverse drug reactions we looked at each of those two types of documents and then we also added observational studies when we were looking at assessing adverse drug reactions.

So the next slide – results as far as efficacy and then the following slide. So I'll first go through just the general number of papers we found. So our initial search found 1,760 papers overall out of all of our searches. Then we reviewed the abstracts, each of the three of us and based on abstracts suggested which papers we thought could be excluded right off the bat versus those that we wanted pulled so there were a total of 429 papers where we pulled the full text of that paper and then after we applied our inclusion criteria still looking at the correct medication, looking up the correct indications. So for instance if a patient was not treated as an outpatient basically they were a hospitalized patient those guys would be excluded. So after applying all of those inclusion criteria we found 110 publications that were finally included in the review and 77 of those were trials where we synthesized the evidence comparing the different [inaudible].

So the next slide…and for each of the indications we'll break this up by adults versus children. And so I'll have one slide that will list the number of trials that we found and then the following slide will have some details about the results found in those trials. So you'll see that things are broken up in terms of direct comparisons versus indirect comparisons. So direct comparisons being one macrolides versus another and we found a limited number of those types of studies and so we then were forced to go to indirect comparisons where if each of the three macrolides was compared to…or was slated against a common comparator then we would include those trials and make an indirect inference about the activity of the different macrolides based on how they performed against these various comparators. Things like [inaudible] and that sort of things. So for CAP in adults direct comparisons there were two trials of azithro AZ versus clarithro CH and then for azithro versus erythro there was one trial. And this was a trial of multiple conditions. There were several of these trials that we found in our search. So these studies included patients with a variety of respiratory tract infections. They may have had sinusitis, pneumonia, that sort of thing. And…but included some subset of patients with the indication that we were interested in. And so this particular trial, although it was the multiple conditions, did have CAP patients. And these multiple conditions trials were…they varied in how well they broke up each individual condition. And then for clarithro versus erythro there were three head-to-head trials and per CAP adults there were no indirect comparison trials that we pulled.

So the next slide. CAP in Adults the Direct Comparison Trials. So in five of the six trials that…those total number of macrolide versus macrolide trial in five of those six trials there was no difference in clinical cure. And obviously when I say no difference I mean no statistically significant difference. And then for microbiologic cure not all six trials reported that. So you'll see that the numbers will vary when you move from clinical cure to microbiologic cure. And so four of those six trials reported microbiologic cure outcomes and there was no difference in any of those trials. And that one trial of multiple conditions this was an example where they didn't break up their outcomes very well by the different indications and so microbiologic outcomes weren't reported particularly for CAP patients, but for the entire population as a whole. And so we just infer that there was no difference for the patients that had CAP.

Now the one of those six trials that where we did find differences was the trial of…or one of the trials of clarithromycin versus erythromycin. So in two of the three trials comparing clarithro with erythro there was no difference in clinical cure. There was though one trial, a fair quality trial that reported a significant difference in clinical response in favor of clarithro. So 89% versus 72% and those figures, which you'll see throughout the rest of this presentation typically are simply a percent of patients that were assigned a positive clinical response. Now in this trial this difference was only in the intent-to-treat populations. So not in the population as a whole and just a note here that many of the patients in that intent-to-treat population were excluded because there was a lack of a definitive diagnosis of CAP—definitive diagnosis of CAP should be based on…made based on the…on the basis of chest x-ray and many of these patients did not have that performed and so you can't definitively say that they truly had CAP.

Next slide. CAP in Children. There were no head-to-head trials of azithro versus clarithro…sorry, three of azithro versus erythro and one of clarithro versus erythro and no indirect comparison trials.

So the next slide going through the direct comparisons in four of four trials no difference in clinical cure reported and just a note here that three of those trials comparing erythro and azithro included three treatment arms. So there was an additional arm with either Amoxicillin or Amoxicillin/clavulanate. But nonetheless there was no difference in clinical cure recorded. And then two of those four trials reported microbiologic outcomes. Most of these patients were infected with a typical pathogen and there was no difference in microbiological spots in either of these two trials between the two macrolides.

So the next slide – Sinusitis in Adults. Direct comparisons – there was one azithro versus clarithro and again this was a trial with multiple conditions. One azithro versus erythro, again, a trial of multiple conditions. And there were no [inaudible] trials comparing clarithromycin and erythromycin. There was however one trial comparing the extended release and the immediate release forms of clarithromycin. So we also looked to see whether there were differences in those two dosage forms. And here's the first indication where we have…where we had common comparators and so we could include these indirect comparisons. So there were ten trials included here that compared the macrolides against either placebo, Amoxicillin or Amoxicillin/clavulanate.

Next slide. Sinusitis in Adults Direct Comparisons. So in the trials comparing two different macrolides. So not the trials comparing the two dosage forms of clarithromycin. There was no difference in clinical cure between any of those macrolides. And then similar results for microbiologic cure where there was no difference in the trials comparing two separate macrolides. Then if we go to the trial comparing the ER and IR forms of clarithromycin there were no differences in clinical cure reported between these two dosage forms in these trials and microbiologic responses were assessed in these particular trials.

Next slide. Sinusitis Adults Indirect Comparisons. So five trials looked at either azithromycin or clarithromycin versus the Amoxicillin/clavulanate acid. And so here we simply report when we are doing our indirect comparisons whether the macrolide differed in clinical or microbiological response from its comparator and so in these five trials neither azithro or clarithro differed in terms of clinical response rate from… [end of Side B]

George Allen: …three of these trials, which happen to look at clarithromycin versus amoxicillin allowed treatment with oxymetazoline nasal spray, which perhaps may have complicated the results.

Next slide. Sinusitis in Children. This was an easy one, I guess. There were no direct comparisons reported at all in sinusitis in children and there were no indirect comparisons either that we found that were…that met our inclusion criteria.

So the next slide just reiterating this, but we found no direct comparisons to trials in children with sinusitis and there were no indirect comparison trials that met our qualification of having a common comparator compared to each of the three macrolides. So there were no studies that we assessed that looked at sinusitis in children.

The next slide. AECB / ABECB. I won't really make a distinction between those two conditions in adults. There were three trials; one of which was a trial of multiple conditions that compared azithro and clarithro. One trial, again, with multiple conditions that compared azithro versus erythro. We found no trials comparing clarithro and erythro and there were four trials comparing the two dosage forms of clarithromycin. In terms of indirect comparisons the only common comparator we found was dirithromycin, which is in fact a macrolide, but it's a macrolide that's not available in the U.S.

Next slide. AECB in adults direct comparisons. In all eight of these trials that are listed on the proceeding page there was no difference in clinical cure between the two treatment arms. And then as far as microbiologic cure all eight of these trials happen to look at microbiologic cure as an outcome and there was no difference in seven of those eight trials. The detail of that one trial that had a difference reported is below. So the trial of azithromycin versus clarithromycin – in all three of those trials there was no difference in clinical cure and in two of those three trials there was no difference in microbiologic cure. However, one trial here found a significant difference…statistically significantly difference in microbiologic response in favor of azithromycin. 93% of patients with bacterial eradication versus 75% of patients treated with clarithromycin showing bacterial eradication of pathogen that infected them as they entered treatment. And one note here that in these trials there was some heterogeneity in terms of the clarithromycin doses. Some trials included 250 mg BID and some trials included 500 mg BID. And then finally on this slide clarithromycin ER versus IR. There was no difference in either clinical or microbiologic response in any of those trials.

Next page. Indirect Comparisons. So here we have our trials that looked at the macrolide versus Dirithromycin and in none of those trials did either azithro, clarithro or erythro differ in clinical response from Dirithromycin.

Next slide. AECB / ABECB in Children. As you can see here in no trials either of direct comparisons or indirect comparisons were found.

In the next slide AECB basically does not exist in pediatric patients. It's not really a recognized entity in pediatric patients and so for that reason it wasn't a surprise to us that we found no trials of AECB in children.

Next slide. Acute Otitis Media in Adults. Direct comparisons – the only one we found here was a trial of azithromycin versus clarithromycin and it was a trial again of multiple conditions. So a multitude of different respiratory tract infections including otitis. And there were no indirect comparison trials found.

Next slide. Talking further about this one trial that we found. It was a fair quality trial that compared azithromycin and clarithromycin and there was no significant difference in either clinical or microbiologic response in this trial. And just a note that the acute otitis media basically is the disease of children and so this explains why we did not find many suitable trials in adults with AOM.

Next slide. AOM in Children. So direct comparisons the only trials we found again compared azithromycin and clarithromycin. We found two trials that compared these two agents. No trials that compared azithro and erythro or clarithro and erythro. And then with indirect comparisons we analyzed five trials that

included the macrolide against amoxicillin and amoxicillin is the gold standard really for treatment of otitis and so this was a suitable indirect comparative we felt.

Next slide. AOM in Children Direct Comparisons. Two of these two trials there was no difference in clinical cure and in microbiologic cure was not assessed in either of these trials. So we only have our clinical response rates to report.

Next slide. Indirect Comparisons in Children. Again, five trials all looking at amoxicillin as a comparator. So in the majority of trials – four of five there was no difference in clinical response between the macrolide and amoxicillin and the microbiologic response, again, was not assessed in any of these trials probably due to the difficulty of obtaining a specimen for microbiologic evaluation in otitis. Now there was one trial of azithromycin versus amoxicillin that found no significant difference in clinical response. However, a second trial of azithromycin versus amoxicillin found there to be a significant difference in favor of azithromycin with 83% of the patients with a positive clinical response versus 60% treated with azithromycin. Again, this is a problem when you have these multiple trials and looking at indirect comparisons there was some heterogeneity in the macrolide doses used in these different five trials.

Next slide. Pharyngitis in Adults. Direct comparisons – two trials of azithromycin versus clarithromycin. One of these was a trial again with multiple conditions. We found no azithromycin versus erythromycin trials and there was one trial of clarithro versus erythro. In terms of indirect comparisons there were seven trials that included a comparison of penicillin, which is again kind of the gold standard for pharyngitis treatment against a macrolide.

Next slide. Direct Comparisons. Again, as we've seen over and over again with these different indications no difference for the most part in clinical cures. So all three of these trials reported no difference in clinical cure between the macrolide. In two of those three trials there was no difference in microbiologic response. So detailing that further if we look at azithromycin versus clarithromycin one trial showed no difference in microbiologic cure; however, one trial which was a fair quality showed a difference in favor of azithromycin and the outcome of that both early follow up and late follow up are listed there. And so the difference in favor of azithromycin compared to clarithromycin at each of those follow up points.

Next slide. Indirect Comparisons. There were no trials that compared erythromycin to penicillin so all that we included here were trials that compared azithro or clarithro to penicillin. So in all seven of these trials there was no difference in clinical response. In six of the seven no difference in microbiologic response. So the one trial that did show a difference was a trial of clarithro versus penicillin that showed a significant difference in microbiologic cure in favor of clarithromycin and that was only at the early follow up. So a late follow up evaluation that difference had disappeared. And one note here is that the penicillin dose used in that trial was 250 mg q8h whereas a more appropriate dose is 250 q86. And so it's possible that that may explain at least in part the reason clarithromycin was superior to penicillin in this trial. And then in these trials there were some trials that included ER form of clarithromycin and some that included the IR forms. So two trials with the ER and four with the IR.

Next slide. Pharyngitis in Children. The two trials that we found that included direct comparisons so one each of azithromycin versus clarithromycin or erythromycin. And in indirect comparisons again penicillin was the comparator that was common to all macrolides. And so that was the one comparative [inaudible] that we included in our indirect comparison evaluation.

Next slide. Direct Comparisons. Again, no difference in clinical cure in either of these head-to-head trials. There was a…this was a case where it depends on what your definition of clinical response is basically. And so this particular study used clinical cure and then also had an outcome of clinical success, which is cure plus improvement. And so in this case there was a difference in clinical cure in favor of azithromycin. So I guess that first line of the slide might be slightly misleading. It should really say clinical success no difference in

two of two trials. And so in this trial of azithro versus erythro there was a difference in clinical cure in favor of azithro; however, [inaudible] value reported. But if you then use the outcome of clinical success, which is cure plus improvement there was no difference between these two treatment arms. Microbiologic cure, again, no difference in two of two trials. In terms of overall microbiologic efficacy. However, there was in one of these trials a modified intent to treat population of 24 patients who did not complete the protocol and in these particular patients there was a difference in favor azithro in terms of eradication of streptococcus pyogenes in particular.

Next slide. Indirect Comparisons in Children. There were nine trials. Looking at penicillin versus either of the macrolides so there was no difference in clinical response in eight of these nine trials and in terms of microbiologic response no difference in two of the nine trials. So there was one trial of erythro versus penicillin that showed a significant difference in favor of penicillin. However, as the next line indicates there was lower than optimal duration of therapy used for erythromycin in this particular trial. And the clinical response rate associated with erythromycin in this trial although it was inferior to that of penicillin it was similar to response rates reported for azithromycin and clarithromycin in the other trials included in this group of indirect comparisons. In terms of microbiologic efficacy in five azithromycin trials there was a difference noted—two of those in favor of azithromycin and then in both of the trials comparing clarithromycin to penicillin there was a microbiologic difference in favor of clarithromycin. This is a case again where there was a great deal of heterogeneity in doses used for both the macrolides and for the penicillin treatment within these trials.

Next slide. MAC Infection. Direct comparisons – with MAC we looked at not only treatments of [inaudible] infection, but also prophylaxis. And so in the direct comparisons arena there were two trials of azithromycin versus clarithromycin and with indirect comparisons there were four trials that included placebo or rifabutin and these only prophylaxis trials.

The next slide. MAC Infection in Adults Direct Comparisons. Primary outcome here is the MAC is of course slightly different from any of the indications we talked about so far. So the primary outcome measure in these studies was sterilization of blood. So one trial showed a significant difference in the sterilization at week 16 in favor of clarithromycin versus azithromycin. There was no difference in mortality reported, however. So the only outcome where there was a difference noted was sterilization of the blood. Another trial there was a physically non significant difference in sterilization at week 24 in favor of clarithromycin. We reported this only because of the statistically significant difference in the trial above. And again in this trial mortality…can't make any conclusions here because mortality was not assessed in this trial.

Next slide. MAC Indirect Comparisons. So there were two trials looking at either azithro or clarithro versus placebo. Both were superior to placebo with respect to time course to subsequent MAC infect. One of these trials reported mortality data and as you would expect there was a significant difference in mortality in favor of clarithromycin. So if we were to, using these two trials, try to make some assessments of the comparative efficacy of azithromycin and clarithromycin we really can't do that because these trials differed widely in terms of study design, etc. So really we just report each of these as a single entity. Then there were also trials of azithromycin or clarithromycin versus either rifabutin or that macrolide in combination with rifabutin [inaudible] trials here. Both azithromycin and clarithromycin were found to be more efficacious than the rifabutin armed by itself. Again, there was a great deal of heterogeneity in terms of these studies and their inclusion criteria and that sort of thing and so we felt that we couldn't make an assessment of the comparative efficacy of azithromycin and clarithromycin.

Next slide. MAC Infection in Children. So again an easy slide here. No trials of either direct comparison interventions or indirect comparisons.

Next slide. Reiterating this point. No trials of either treatment or prophylaxis of MAC were found in children.

So the next slide. Unless there are any questions at all on any of the clinical outcomes at this point? Okay. So results for adverse drug reactions. So now on the slide where the title is ADR. So, again, just to reiterate what I had talked about already. We looked at overall adverse event reports. So percent of patients that had a given adverse drug reaction in each of these trials. Also the number of withdrawals due to an ADR. serious ADR and then again specific ADR are listed there. The primary adverse drug reaction that we assessed because it was the most widely reported were the gastrointestinal adverse reactions. Although we were interested in looking at the comparative incidence of QT interval prolongation and ventricular arrhythmias. It's such a rare adverse drug reaction that we couldn't make an assessment of that based on the trials that we looked at. In all of the randomized control trials that we evaluated none of them include any reports of this adverse drug reaction of QT interval prolongation / torsades de pointes, etc. So based on the evidence that we have here we really are uncertain as to the comparative ability of these three macrolides to cause this adverse drug reaction. However, there was a review performed in 2002 of MedWatch reporting which found the relative risk of arrhythmias with the three macrolides to be as follows: most frequently reported was clarithromycin followed by erythromycin and then lease frequently reported with azithromycin. However, there obviously are limitations to review of MedWatch program data.

Next slide. Gastrointestinal and Other Adverse Drug Reactions. And again by far gastrointestinal reactions were the most commonly reported. So in two trials looking at placebo versus macrolide the rate of study withdrawal was greater for daily clarithromycin versus weekly azithromycin in MAC prophylaxis. However, neither macrolides differed from placebo in terms of study withdrawal rates. And then if we look at…we'll go through the different macrolides in head-to-head form. So this will be a study of just all the studies that we've talked about up to this point. So in 11 trials of azithromycin versus clarithromycin overall there was no difference in adverse drug reaction in terms of percent of patients who had particular adverse drug reactions. One study did find a significant difference in terms of patients who withdrew from the study in favor of azithromycin.

Next slide. Azithromycin versus Erythromycin. In three of the six trials there was a significant difference in ADR in favor of azithromycin and the numbers are listed there. Again, these would be patients…overall percent of patients who reported an ADR and the common theme here, most of them reported were GI in nature and some studies would perform an analysis of comparative rates of each specific GI adverse reaction. So diarrhea, etc. In the two treatment regimens but this particular…these particular studies did not do that. And the rate of study withdrawal did not differ in any of these six trials comparing azithromycin and erythromycin.

Next slide. Clarithromycin versus Erythromycin. Two of these five trials a significant difference in favor of clarithromycin. Again, most of these were GI in nature. And here we had some studies that did do kind of a subgroup analysis of specific GI adverse reactions. And again in three of the four that did this there was a significant difference in favor of clarithromycin. A fourth…the fourth of these trials reported a trend, but not a statistical study in difference in favor of erythromycin. Three trials did find there to be a significantly higher proportion of patients who withdrew from the study in the erythromycin arm versus the clarithromycin arm.

Next slide. Extended Release versus Immediate Release Forms of Clarithromycin. In five trials that we looked at there were…was no significant difference in adverse reactions between these two formulations. Down at the bottom of the slide we have kind of a synthesis of the adverse reaction reports from all of our indirect comparison trials and…so basically what we report here are just the overall rates of adverse drug reaction reported. And so you see that they varied wide with azithromycin ranging from 4% to 36% and clarithromycin 4% to 58% and erythromycin 2% to 100%. We record these as overall ADR rates, but obviously making comparisons between the three macrolides based on these indirect comparisons is problematic.

Next slide. Subgroup Analysis. So again just reiterating this from the beginning of the presentation. The subgroups that we evaluated were demographics – age, gender, ethnicity, concomitant medication, co-morbidities and pregnancy. So the question was, "In any of these subgroups does one macrolide differ from the other?" And we found there to be no evidence whatsoever to suggest that one of the macrolides was superior to any of the others in these particular subgroups nor did we find that they were associated…that one macrolide was associated with more ADR than was another in these particular subgroup analyses.

The next slide will summarize what we found. So for efficacy – the next slide. In terms of the outcomes we looked at as I mentioned earlier there were few trials included that looked at the outcomes of percent switch to alternate antimicrobial, rate of hospitalization, and/or mortality. So we were limited basically to looking at clinical efficacy and microbiologic efficacy. We feel that overall there are limited assessments that we can make of the relative clinical or microbiologic efficacy of azithromycin, clarithromycin and erythromycin for any of the indications that we included in our analysis. One reason for this would be the relative lack of direct comparison trials that we found and then again the problems in comparing indirect comparison trials and making an assessment of the macrolides based on those trials. One note about MAC infection. erythromycin has minimal activity against MAC and so that was why erythromycin was not included in any of the trials looking at MAC infection or prophylaxis.

Next slide. Adverse Drug Reactions. As I mentioned, and as is common with the macrolides most adverse drug reactions were gastrointestinal. And again we couldn't make any assessments of the risk of arrhythmias between the three agents. And overall it appeared to be that erythromycin was associated with a greater incidence of adverse drug reactions than either azithromycin or clarithromycin. And there is a mechanistic basis that would support that finding in terms of GI adverse drug reactions. However, we felt that a comparison of azithromycin versus clarithromycin in terms of overall adverse drug reaction risk could not be made based on the evidence that we had.

Again, subgroup analysis. There was no evidence to suggest any difference between the three agents with respect to their efficacy or risk of adverse drug reactions in any of the subgroups that we looked at. And finally, a few unresolved issues that are sort of outside the scope of simply looking at these…looking at the evidence found in randomized clinical controlled trials, but that we think are important issues when looking at the macrolides – one would be drug interactions. So there certainly are differences in drug interaction profile between these three agents and there is a section of our report that includes drug interaction information and there is always the issue of compliance, as well, which we didn't for the most part assess because most trials that we looked at did not report compliance rates. But that is of course always a consideration. And the differences in anti-bacterial spectra; this is discussed in the beginning of our report and the major issue here is that erythromycin lacks activity…relatively lacks activity against [inaudible] influenza A. And so in terms of impaired treatments of respiratory types of infections I did the whole that erythromycin has. And then bacterial resistance we did not assess this globally, but it's important to note that resistance rates have risen over time and so if you look at an older trial looking at erythromycin and comparing that to a newer trial with either of the other two agents or of erythromycin there certainly might be differences since resistance has increased over time.

So then the next slide…so, again, I'm George Allen and I'm here and then Dr. Bearden is here and Michelle Liedtke and we'll take any questions if you like.

Carol Cordy: Thank you. Any questions?

T. Vyn Reese: Hi, this is Dr. Reese. Can you hear me?

George Allen: Yes.

T. Vyn Reese: Okay. The drug interaction point is not trivial. I mean the 384 drug interactions with erythromycin can be quite severe and fatalities have been reported in case reports certainly at least for several drugs, including the HMG-CoA inhibitors. I want to have you comment a little bit more about the relative risks between the drugs and those types of drug reactions, which can have fatal outcomes.

George Allen: I certainly agree that it's not a trivial point and the reason that we didn't talk about it further is that it's really impossible or next to impossible to assess when analyzing these clinical trials because of course they'll exclude patients who are on any medication that would interact. So we couldn't really make any assessment from a systematic point of view, but when you're talking about Cytochrome P450 interactions and 384 erythromycin is the most potent inhibitor. Clarithromycin is next most potent and azithromycin essentially has no inhibitions of Cytochrome 384. And so you really, I think, based on a certain…a great amount of evidence you can definitely make an assessment that the order of being an offender, I guess, in terms of adverse drug reactions would go erythro, clarithro, azithro.

T. Vyn Reese: One other question I had. You didn't talk about the treatment for Helicobacter Pylori and that's where clarithromycin is commonly used and azithromycin has no indication. Can you comment briefly there? That's another important treatment where we actually have to, you know, write every day.

George Allen: The only comment I could make, I guess, was that I think we did discuss that as a potential indication when we were developing our key questions and it wasn't included as one of the indications that we looked at. So I certainly couldn't make any kind of an assessment of how the different drugs compare in clinical trials, but I guess I would just say that there are indications for macrolides that we didn't look at and so from your point of view I guess it is reasonable to take those indications into account.

T. Vyn Reese: Okay. Thank you.

George Allen: So we didn't personally look at those other alternative indications. Thank you. Any other questions?

Carol Cordy: Could you stay for just a minute? Are there any stakeholders? There were none signed up. Okay. I just wanted to make sure. Any other questions? I guess not. Thank you very much. Wait a minute, maybe there is one.

Man: I don't have a question, I just have a comment. Maybe we have to enter that very key question on the next round for the Helicobacter Pylori because I think that would really be…

T. Vyn Reese: I have another question of the committee. This is the first antibiotic we've reviewed and so that's like…it's a totally different animal. I mean this is not like the other chronic medications that we've reviewed because if you [inaudible] to a therapeutic interchange or you stop, you know, one prescription the patient doesn't get treated if they have a serious infection like CAP they may have a very bad adverse outcome. So it's a very tricky area. Antibiotics are very tricky to therapeutically interchange and to control in this manner. So I think we have to be very cautious. Plus there are multiple indications for these drugs. It's a very heterogeneous group and there're indications that aren't, you know, that they don't all have. Like some are indicated for MAC, others aren't. Some are for H Pylori, others aren't. Some have major drug interactions with other drugs that are commonly prescribed and the others don't. So it's a very complex group given all those considerations. There's clearly a drug that's probably the best of this group, but that doesn't cover everything. So it's…that's my comment. This is not an easy decision to make and I think we'll have to…when we're writing this out we're going to have write all the different exceptions, which are…there are legion.

Carol Cordy: I wonder if it would help or be possible for the people that prepared this report to stay around for our discussion? Is that possible? Can you stay a few minutes?

George Allen: Yeah, sure.

Carol Cordy: I think as we work through trying to formulate a motion on this we may need some guidance.

George Allen: Yeah, we're all available.

Carol Cordy: Okay. Thank you.

Patti Varley: This is Patti Varley. As I listen to you say that my other concern, I guess, I'll put out here which is to the best of my knowledge unless it's different in antibiotics I'm not sure people always write what diagnosis they're writing that prescription for. So that, to me, raising a concern as far as interchange in regard to how would the pharmacy know what you were treating with that particular antibiotic if it's not always indicated on the prescription?

George Allen: I think you're right in most cases one wouldn't know what the indication is and so you would just have to rely on, I guess, [inaudible] prescribing level that it was done appropriately in terms of indications and giving the appropriate [inaudible]. Certainly when the prescription was presented that would not be known.

Patti Varley: Right. I'm thinking even if you ask the patient they may not know.

George Allen: Yeah, true.

Carol Cordy: Is there more discussion? Maybe we should just try and make some kind of a motion and work off that so we know what our issues are. Somebody want to give that a try?

Patti Varley: I know you want me to do this, Carol. This is Patti Varley. Well, I'll go ahead and read what's up there and then we can discuss it. After considering the evidence of safety, efficacy and special populations for the treatment of community acquired pneumonia, acute bacterial sinusitis, acute exacerbation of chronic bronchitis, acute bronchitis, acute otitis media, pharyngitis, and mycobacterium avium complex infection, I move that…and I'm not going to be able to pronounce those three correctly. So azithromycin, clarithromycin and erythromycin are safe and efficacious. No single macrolide is associated with fewer adverse events in special populations. And that's I think where…I think we do need to amend that because of some of the discussion we had earlier. And I'm not quite sure how to say it in regard to adverse reactions when on other medications. And I…does anybody want to help me out with that? Because I don't think that statement's accurate.

T. Vyn Reese: Yeah, that statement is not true. Special populations who are on other drugs that interact with erythromycin and clarithromycin need to be excluded and if there's an erythromycin indicated or macrolide indicated in those drugs it would be azithromycin. So azithromycin…you go all the way down to safe and efficacious and you'd have to say that azithromycin must be on the Washington State Formulary, but also clarithromycin has to be on for Helicobacter Pylori. Okay? So it has to be on two. And erythromycin, if you don't have a drug interaction, you're young and healthy and you don't get diarrhea from it is a fine drug. So I don't see a reason that we should…there's indications for all of those and unless you know the diagnosis you can't limit or therapeutically interchange the drugs. That's my problem with this group.

Patti Varley: I agree with you. The question is, "How do we…I mean do you just say they can't be interchanged and they're all on there?" Or do we need to clarify within this motion those specific idiosyncrasies that you just described?

T. Vyn Reese: Good question.

Patti Varley: I mean if you say they're all on the list and you say they can't be interchanged do you cover your bases or do we need to clarify out and spell out those specifics? The reason I'm struggling with this has to do with the question I raised earlier, which is that a prescription is not going to present itself to a pharmacy with a diagnosis on it. So it's not that that criteria…or that is going to be utilized in regard to the filling of that prescription. And that's where I'm struggling.

T. Vyn Reese: I think we have to have all three on as Bob said. I think we have to have all three on. I don't see how you can make the diagnosis be written onto the prescription and have the correct drug…another drug be substituted for a drug that only has that narrow indication. So it's very tricky. Plus if somebody has a major drug interaction you can't force them to therapeutically interchange clarithromycin for azithromycin if azithromycin is the safer drug for somebody who's on a Statin. So it's…I think they all three have to be there. And erythromycin is a drug that's been out for a long time and is safe if somebody is healthy, young and has a strong bowel.

Jeff Graham: Carol, this is Jeff Graham. I think that probably Dr. Allen and staff they could probably go.

Carol Cordy: Okay. Thank you. I think we'll struggle through this ourselves. But thank you for your presentation.

George Allen: Anymore input from us you want at all or…

Carol Cordy: Are there any other questions? It looks like not. But thank you very much.

George Allen: All right. Thank you.

Woman: Dr. Cordy?

Carol Cordy: Yes.

Woman: I am just going to throw out a suggestion. Is there a possibility that we could…could identify these by diagnosis and think of this in terms of step therapy or expedited prior authorization? Just again, to get us thinking in terms of that.

Carol Cordy: I wanted actually to make one comment. I think the fact that clarithromycin is used for H Pylori I don't think we need to consider that here because that's not one of the diagnostics that we're looking at. So I think we cannot necessarily have to include that on this.

T. Vyn Reese: But Carol the thing is that they won't put the diagnosis down. So you won't know those cases.

Carol Cordy: Well, but if we were…

T. Vyn Reese: That are being treated or used to be treated H Pylori unless we make people write them down and it's commonly written, you know, the same. Those for bronchitis would be for H Pylori. Of course it would be written with two other drugs.

Carol Cordy: Yeah, but I just want to…if we're saying…if we do agree that they cannot be subject to therapeutic interchange then that wouldn't be a problem.

T. Vyn Reese: No, that wouldn't be a problem. She's saying that we…and if there was some way we knew the diagnosis you wouldn't want people to automatically pick the most expensive one for bronchitis or something when a lesser one would do. But if you don't know the diagnosis then you can't do that. That's the problem. I think getting providers to write the diagnosis on the prescription is going to be a struggle.

Carol Cordy: So it sounds like, unless there's something else, that the two issues that I've heard so far are the problem with drug-drug interactions, which we somehow need to put in there and the problem with keeping clarithromycin available for people with specific diagnosis of H Pylori. Are those the two? So it's how to incorporate that into the motion.

Duane Thurman: This is Duane. Can I suggest? I mean I want to be careful here that the staff is not, you know, interfering or guiding your decision. I think you should make your decision based on what you see is the evidence based before you to the extent that, you know, this is the first review of this class. We do have the option of monitoring and trying to develop data. This is not the last decision. So I would just encourage you to do what you feel that you need to do based on this evidence to give us directions in terms of what drugs you think should be included on the Preferred Drug List. And, you know, I think once you start defining every indication we're going to be here until the next updated review.

T. Vyn Reese: Yeah, I agree and I think we should probably have all three drugs on given what we've already talked about and not go into every…when each one is individually indicated and when the other ones aren't indicated or there may be a drug interaction or something else where you couldn't use it. I mean if we start doing that we will be here all night.

Duane Thurman: And then I think from the agency perspective I think that's what we intend to do is that we need to continue to try to develop the kinds of data we can collect. Siri mentioned earlier today that they are shifting over to another computer system that will have greater capabilities. This just sets the basis for us to begin to move into this kind of a class of drugs.

Woman: Let me try one other thing without leading the committee. There are several different dosage forms for each of the antibiotics, too. So, you know, that might be some of the consideration, as well.

T. Vyn Reese: There's not been any evidence presented to the committee that the dosage forms have anything to do with how active the drugs are. And so the dosage forms, you should pick the dosage form that's the least expensive, obviously for all these drugs because there's no difference, you know, the longer time released dosing forms have no…there's no evidence [inaudible] they are more effective. They might be more convenient, but they are not more effective.

Janet Kelly: This is Janet Kelly. I think the one piece that maybe we're missing is that it's not true for all of the indications, but a lot of times you can tell the indication by the dose for some of the things. That helps. That doesn't help for all of them, unfortunately. So that's where…I mean if all of them you could tell what the

indication was strictly by the way you dose it that would make things a whole lot easier. That's true of a few of the, but not all of them.

Jason Iltz: This is Jason. Siri, I wanted to ask a question in regards to this new system that's coming down the pipeline. Are you are of the edits that can be put in and, I mean, what sort of things can be included? I mean I'm just sort of thinking sort of outside the box a little bit saying, you know, if we were to say, you know, as you mentioned, Vyn, this is sort of a heterogeneous group with some differences here and there, but if we were to say that all available generic formulations of these medication should be on the formulary and then have some sort of that subpopulation identify it again where…because I believe clarithromycin is still branded or are they all?

Donna Sullivan: This is Donna Sullivan. There are generics for all of the products.

Jason Iltz: All of them now?

Donna Sullivan: Yes. The suspension for Zithromax just came out.

Jason Iltz: Okay. My other thought was if it's tied to other medications that are filled so, I mean, certainly there's different…there's different H Pylori regimens that are out there and so you're never going, unless it's prescribed incorrectly, you're never going to have clarithromycin just by itself. So given that are those edits that can be made? I mean I'm just trying to figure out how this system works without a diagnosis. Are there other things that we can work with? [end of Side A]

[Side B]

Siri Childs: …to look for specific drugs that would mean a specific diagnosis. But we don't have that case in all of the antibiotic use of these, you know, but for a few of them we could do that. Now and certainly in the new system if we had a diagnosis in the computer from office visit in the future, you know, we can have it come across so that we would have diagnosis' to hit against as well. So the new system will enable us to do a lot of this and this drug class probably won't be implemented. What's our schedule to implement this drug class?

Woman : January 1st.

Siri Childs: Oh, okay. Step therapy.

T. Vyn Reese: This is Dr. Reese. If we just left it this way you could use the generic formulations of all those drugs and be fine. You could use the generic formulations of all those drugs and be fine. We didn't say you had to use some certain long-acting drug or some brand name drug. We just said these drugs should be there. I think just leaving it simple would be the best way instead of putting in all the exceptions and special indications.

Carol Cordy: This is Carol Cordy. I'd like to try though just throwing in a modification to the one sentence after it says safe and efficacious. Say because of differences and we can erase this if you want. Because of differences in adverse drug reactions and drug-drug interactions erythromycin, clarithromycin, and azithromycin must be on the Washington Preferred Drug List just as an explanation for why the committee is feeling like they all three need to be there.

Man: Would you mind leaving generic in there?

Carol Cordy: Well, you can throw in generic. That was just added after. Yeah, the generic formulations.

Bob Bray: This is Bob Bray. I think that's accurate, but I think we also want to add because of differences in spectrum and indications.

Carol Cordy: Okay. Indications, adverse drug reactions and drug-drug interactions. Is that good? But do we need that…the dose would be based on the disease. Right?

T. Vyn Reese: azithromycin is not capitalized. It should…it's not a branded name. That's a small point.

Bob Bray: This is Bob Bray. I just want to make an editorial comment. I would support this and think that looks good, but I'm very concerned about doing anything that results in a prior authorization when the patient needs to get an antibiotic and, you know, I could see there being a hang up, the person not getting the antibiotic and a hospitalization result instead of an outpatient management because of them getting worse because of delays in getting antibiotics. So I think that…that's more a comment for when we do this in the future for other antibiotic classes. I think we have to be very, very cautious about anything that might set a barrier in front of a patient who has an urgent need for an antibiotic to be started.

T. Vyn Reese: Bob, if it's written this way they should get any of those three. But I agree, I agree in the future this is…antibiotics are very tricky and they have…a lot of them have several indications and some in the same class don't have the same indications and so you've got to be very cautious when you're talking about the antibiotic drug classes that you don't force a patient to get a drug that's not safe or doesn't treat their condition or that is, you know, that there is a delay. If you wait two or three days before they get their drug and they have pneumonia they may not be here.

Carol Cordy: I have a question. Why was this particular group of antibiotics looked at? Is it a trial run? Is it easy? Are there just three?

Duane Thurman: This was the legislature, you know, the original project was for about 27 drug classes to be reviewed and they thought this was such a wonderful idea that they would throw in a budget note and say, "Why don't you do another 50 and we'll assume that you're going to save all this money," and we did an analysis and one of the differences here is this is the first drug class review that we've had to do solely as the State of Washington. So we were not able to take into account the economy's [inaudible] scale of having all the consortium participants that work with the dirt project. And so we had to go back and tell them because they had appropriated funding for the reviews and say that we can do X number of reviews, I believe there are two—this drug class and another where the cost of doing the review would not exceed the savings resulting from the review. And so it was sort of a…too much of a…you know when we're successful they want to make sure that we take that and exploit it as much as possible and we had to go back and say, "You know, 50 drug classes is not a…you don't have infinite savings." So this doesn't fit well, but we did what we were told to do and we will try to do what we can.

Carol Cordy: Makes sense.

Jeff Graham: Well, actually, Duane, this is Jeff Graham. Our last meeting we did nasal corticosteroids. We did that on our own. And so this class we began to look at what we thought we could do and we thought, well, if we can get to the…where we are right now that would be the best we could probably do.

Duane Thurman: And we're currently talking about the next phases of what the project will look like going out into the future and, you know, I suspect that will be a combination of some new drug class reviews, but also some emphasis on re-reviewing and updating and getting that into a process so that our PDL remains up-to-date.

Carol Cordy: This is one that is clearly not going to save a lot of money. Or any.

T. Vyn Reese: We did say generic. It will save some. Can we just go ahead and make a motion and lay this thing to rest? This is like a sloppy thing here. After considering the evidence of safety…I don't know even know…whose motion was this?

Patti Varley: It was mine.

T. Vyn Reese: Finish it off.

Patti Varley: Do I have to say those words again? This is Patti Varley. After considering the evidence of safety, efficacy and special populations for the treatment of community acquired pneumonia, acute bacterial sinusitis, acute exacerbation of chronic bronchitis, acute bronchitis, acute otitis media, Pharyngitis and mycobacterium avium complex infection, I move that azithromycin, clarithromycin, and erythromycin are safe and efficacious. Because of differences in indications, spectrum of activity, adverse reactions and drug-drug interactions, the generic formulations of all three must be preferred on…must be on the Preferred Washington…oh, what a minute. Must be preferred on the Washington Preferred Drug List. Macrolides cannot be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of conditions listed above.

Jason Iltz: This is Jason. I'll second it.

Carol Cordy: All in favor?

Group: I.

Carol Cordy: Opposed? The motion passes.

Duane Thurman: Dr. Cordy, if I could just say one thing. I think today's meeting we had our Director for the Health Technology Assessment Program that the legislature passed largely on the success of what's happened here and I think it's interesting because I think things…we've been doing this quite a while and I think we're finally now following into the…I mean this was good. I think it set a permitable standard and sent our new Director away afraid because she's got to set something like this up in a more…an environment where the evidence is even worse. I just want to thank you all again for taking the time to do all of this and to really do the review, you know. The comments from the Pfizer rep, I talked to him briefly at lunch and I made it very clear that we do have the reports, we do read the reports and they are in front of that. And I know how much work that is and I really appreciate that.

Carol Cordy: Thank you. So we are adjourned until October 18th. Same time, same place?

Man: So far.

Carol Cordy: As far as you know. Okay. [end of Side B]